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OF

THE MIDDLESEX HOSPITAL

VOLUME V

Fourth Report

FROM THE

Cancer Research Laboratories

THE CANCER WING, THE MIDDLESEX HOSPITAL

London
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1905

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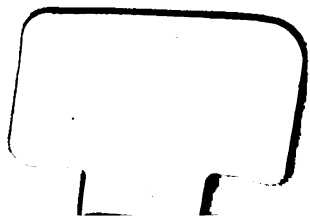

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OF

The Middlesex Hospital

VOLUME V

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Archives of The Middlesex Hospital.

THESE Archives are published with the object of recording work done in the Wards, Laboratories, and Special Departments of The Middlesex Hospital, and contain contributions upon subjects connected with—

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2. The Investigation of Cancer,
3. Research carried on in the Pathological and Bacteriological Laboratories, and
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ARCHIVES

OF

THE MIDDLESEX HOSPITAL

VOLUME V

Fourth Report

FROM THE

Cancer Research Laboratories

EDITED FOR THE CANCER INVESTIGATION COMMITTEE

BY

W. S. LAZARUS-BARLOW, M.D., F.R.C.P.,

DIRECTOR OF THE CANCER RESEARCH LABORATORIES; FOREIGN MEMBER OF THE GERMAN COMMITTEE FOR THE INVESTIGATION OF CANCER; FORMERLY PATHOLOGIST AND LECTURER ON PATHOLOGY AT THE WESTMINSTER HOSPITAL

London

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NEW YORK: THE MACMILLAN COMPANY

1905

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(1905).

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BOSTON MEDICAL
JUN - 1906

EDITORIAL NOTE.

IN the present Volume are included the details of all cases that were microscopically diagnosed as malignant disease, and were admitted into the Hospital—whether the General Wards or the Special Cancer Wards—during the year 1904. In addition, Papers on various aspects of Cancer have been contributed by the Staff of the Laboratory and others.

The present volume is largely statistical, and the plan of introducing papers dealing in detail with special seats of malignant disease in the light of the records of the Hospital will be continued in future Reports. In this way not only will the large store of material accumulated at the Hospital since 1747 be utilized, but also a sound basis will be laid for future work.

I have much pleasure in acknowledging the cordial assistance which has been given me during the past year by all my colleagues in the Laboratories.

W. S. LAZARUS-BARLOW.

CANCER RESEARCH LABORATORIES,
THE MIDDLESEX HOSPITAL, LONDON.
March 25th, 1905.

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NOTICE.

In the following pages, excepting where an asterisk (*) *is placed, or where the context makes it clear that such is not the case,* EVERY DIAGNOSIS OF MALIGNANT DISEASE HAS BEEN MADE AS THE RESULT OF MICROSCOPIC EXAMINATION.

W. S. L.-B.

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REPORTS

FROM THE

CANCER RESEARCH LABORATORIES.

TABULATED SYNOPSIS OF THE POST-MORTEM EXAMINATIONS AND OPERATIONS IN CASES OF MALIGNANT DISEASE DURING THE YEAR 1904.

By W. S. LAZARUS-BARLOW, P. CAMPICHE, H. COLWELL, W. GORDON TAYLOR.

In the following tables are given the results of all cases of malignant disease—as determined by microscopical examination—which were investigated in the Cancer Research Laboratories during the year 1904. The material was derived partly from the post-mortem room and partly from the operating theatre. In seven cases the same individual appears in both lists, having been operated upon and having subsequently died in the hospital within the year 1904. Subtracting these from the combined totals of Tables I. and II. it is seen that during the year 265 cases were microscopically demonstrated to be the subject of one or other variety of malignant disease. All of these were in-patients. A certain number of out-patients with malignant disease also came under observation notably in the Electrical and Cancer Out-patient departments. In the great majority of these cases the diagnosis was not ratified by microscopic examina-

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tion, and since a microscopic examination is regarded as fundamental for the purpose of these reports they have not been included in the present tables and figures. Nevertheless the cases dealt with in the Electrical Department are made the subject of a communication by Mr. C. Lyster in the present volume.

Of the 265 cases of malignant disease 85 affected males, 180 affected females. The total number of admissions to the Hospital during 1904 was 3,695; viz., 1,749 males, 1,946 females.

It may be repeated here in respect of all cases, that organs in which the diagnosis was made macroscopically, but in which a microscopic examination was wanting, are distinguished by an asterisk (*).

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TABLE I.

Post-mortem Cases.

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TABLE I.—

		Total.		0—5.		6—10.		11—15.		16—20.		21—25.		26—30.		31—35.	
		M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
	CARCINOMA.																
Alimentary System.	Lip ... ... Squamous	4	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Cheek ... ... Squamous	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Tongue and floor of Mouth ... ... Squamous	6	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Tonsil ... ... Squamous	3	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Larynx ... ... Squamous	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Œsophagus, Middle part Squamous	7	0	—	—	—	—	—	—	—	—	—	—	1	—	—	—
	„ Lower part Spheroidal	1	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Stomach, Cardiac end ... Spheroidal	0	1	—	—	—	—	—	—	—	—	—	—	—	—	—	1
	„ Middle ... Spheroidal	0	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	„ Middle ... Columnar	1	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Colon : Ascending ... Columnar	1	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	„ Sigmoid Flexure Columnar	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Rectum ... ... Transitional	0	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Rectum ... ... Columnar	5	0	—	—	—	—	—	—	—	—	—	—	1	—	—	—
	Liver and Bile Passages Spheroidal	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Liver and Bile Passages Columnar	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Pancreas ... ... Spheroidal	0	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Uro-Genital System.	Prostate ... ... Spheroidal	1	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Scrotum ... ... Squamous	2	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Bladder ... ... Squamous	1	0	—	—	—	—	—	—	—	—	—	—	—	—	1	—
	Uterus, corpus... ... Spheroidal	0	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Uterus, corpus... ... Columnar	0	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	„ cervix ... ... Squamous	0	25	—	—	—	—	—	—	—	—	—	—	—	—	—	3
	„ cervix ... ... Columnar	0	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	„ cervix ... ... Spheroidal	0	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Vagina ... ... Squamous	0	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Vulva ... ... Squamous	0	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Breast ... ... Spheroidal		0	20	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Other site ... ... Squamous		0	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Proliferating Cystadenoma...		0	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Ovary ... ... Spheroidal		0	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	SARCOMA.																
Mixed-cell		3	3	—	Glands	—	—	—	—	—	—	—	—	—	—	—	—
Round-cell		0	1	—	—	—	—	—	—	—	Mandible.	—	—	—	—	—	—
Spindle-cell		1	3	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Melanotic		2	1	—	—	—	—	—	—	—	—	Eyelid	—	—	—	—	—
Endothelioma ... ... Lymphatic		0	4	—	—	—	—	—	—	—	—	—	—	—	Peritoneum.	—	—
		45	87														

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Post-Mortem Cases.

36—40.		41—45.		46—50.		51—55.		56—60.		61—65.		66—70.		71—75.		76—80.		81—85.	
M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
—	—	—	—	—	—	—	—	—	—	2	—	1	—	—	—	—	—	1	—
—	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—	—	1	—	—
1	—	—	—	1	—	1	—	2	—	1	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	2	—	—	—	1	—	—	—	—	—	—	—	—	—
—	—	—	—	—	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—
—	—	1	—	2	—	—	—	—	—	3	—	—	—	1	—	—	—	—	—
—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—
—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	1	—	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—
—	—	—	—	—	—	1	—	—	—	2	—	1	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—
—	—	—	—	—	1	—	—	—	—	1	—	—	—	—	—	—	—	—	—
—	—	—	—	—	1	—	—	—	—	—	1	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	1	—	—	—	—	—	1	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	2	—	—	—	1	—	—	—	—	—	—	—	—	—	1	—	—
—	—	—	—	—	—	—	—	—	1	—	1	—	—	—	—	—	—	—	—
—	4	—	2	—	6	—	3	—	5	—	—	—	1	—	1	—	—	—	—
—	1	—	2	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—
—	4	—	4	—	2	—	—	—	3	—	2	—	2	—	3	—	—	—	—
—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	2	—	2	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	Bronchus.	—	Stomach	—	—	—	Kidney	Ovary; Breast	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1 Uterus.	—	—	—	—	—	Stomach Thyroid.	Bladder	—	—	—	—	—	—	—	—	—	—	—
—	—	—	Thigh	Shoulder.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	Maxilla	—	—	—	Colon	—	Breast	—	—	—	—	—	—

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TABLE II.—

	Total.		0—5.		6—10.		11—15.		16—20.		21—25.		26—30.		31—35.	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
CARCINOMA.																
Face ... ... Squamous	1	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Alimentary Canal: Lip ... ... Squamous	9	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Alimentary Canal: Tongue... ... Squamous	10	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Alimentary Canal: Intestine ... Columnar	2	4	—	—	—	—	—	—	—	—	—	—	—	—	—	1 (rectum)
Generative System: Squamous	2	9	—	—	—	—	—	—	—	—	—	1 (cervix)	—	—	—	1 (cervix)
Generative System: Spheroidal	0	2	—	—	—	—	—	—	—	—	—	—	—	—	—	1 (ovaries)
Generative System: Columnar	1	4	—	—	—	—	—	—	—	—	—	1 (ovary)	—	—	—	—
Breast: Spheroidal	1	48	—	—	—	—	—	—	—	—	—	—	—	—	—	3
Breast: Columnar	0	3	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Other Sites ... Squamous	2	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—
RODENT CANCER	5	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—
PROLIFERATING CYSTADENOMA	0	5	—	—	—	—	—	—	—	—	—	1 (ovary)	—	1 (ovary)	—	—
SARCOMA.																
Mixed-cell	1	2	—	—	—	—	—	—	—	—	1 (tibia)	—	—	—	—	—
Round-cell	2	1	—	—	—	—	—	1 (femur)	1 (testicle)	—	—	—	—	—	—	—
Spindle-cell	2	3	1 (kidney)	1 (jaw)	—	—	—	—	—	—	—	—	—	—	—	1 (uterus)
Giant-cell	3	0	—	—	—	—	—	—	1 (jaw)	—	1 (tibia)	—	—	—	—	—
Melanotic	1	2	—	—	—	—	—	—	—	—	—	—	—	—	—	1 (heel)
Endothelioma...	1	8	—	—	—	—	—	—	—	—	—	—	—	—	—	1 (breast)
	43	97	TOTAL NUMBER OF OPERATION CASES FOR MALIGNANT DISEASE ... ... (Carcinoma—Males 33, Females 81; Sarcoma „ 9, „ 8; Endothelioma „ 1, „ 8).													
NON-MALIGNANT.	3	12	—	—	—	—	—	—	1	1	—	1	1	—	—	—
	46	109	TOTAL NUMBER OF OPERATION CASES EXAMINED IN CANCER LABORATORIES.													

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Operation Cases.

36—40.		41—45.		46—50.		51—55.		56—60.		61—65.		66—70.		71—75.		76—80.	
M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—
—	—	—	—	2	—	1	—	2	—	1	—	1	—	—	—	2	—
1	—	—	—	1	—	2	1	2	—	3	—	1	—	—	—	—	—
—	—	1 (rectum)	—	—	2 (rectum, sigmoid)	—	—	—	—	1 (rectum)	1 (colon)	—	—	—	—	—	—
—	—	—	3 (vulva, vulva, cervix)	—	—	—	1 cervix)	—	1 (vagina)	—	—	2 (penis, scrotum)	1 (cervix)	—	1 (vulva)	—	—
—	1 (ovaries)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1 (uterus)	—	1 (cervix	—	—	—	1 (uterus)	—	—	—	—	1 (prostate)	—	—	—	—	—
—	4	—	7	—	8	1	4	—	9	—	9	—	2	—	1	—	1
—	1	—	—	—	1	—	1	—	—	—	—	—	—	—	—	—	—
—	—	1 (cervical gland)	1 (dermoid of neck)	—	1 (jaw)	—	—	—	1 (jaw)	1 (leg)	1 (anus)	—	1 (face)	—	—	—	—
1 (face)	—	1 (eyelid)	—	—	—	1 nose)	—	—	—	1 (nose)	—	—	—	—	—	1 (nose)	—
—	1 (ovary	—	—	—	—	—	2 (ovary)	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	1 (thyroid)	—	1 (parotid)	—	—	—	—	—	—	—	—
—	—	—	—	—	—	1 (nose)	—	—	—	—	—	—	—	—	—	—	—
—	—	1 (gluteus muscle)	—	—	—	—	1 (thyroid)	—	—	—	—	—	—	—	—	—	—
—	—	1 (maxilla)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	1 (skin)	—	—	1 (eye)	—	—	—	—	—	—	—	—	—	—
—	—	—	2 (breast ovary)	—	2 (breast)	—	2 (clavicle, thigh)	—	—	—	1 (breast)	—	—	1 (gland)	—	—	—
—	1	—	2	—	2	—	3	—	1	1	—	—	1	—	—	—	—

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TABLE III.

Synopses of Post-mortem Cases.

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
1	J.J. van D. 159/04	F	76	Squamous cell carcinoma of antrum extending to cheek.	Liver.	Extensive atheroma of aorta. Multilobular cirrhosis.	(ii) Fairly nourished.	(i) 2 Feb. '04. (ii) 11 July '04.
2	F.D. 265/04	M	56	Squamous cell carcinoma of face.	Lymphatic glands.	Chronic renal fibrosis.	(ii) Slight wasting.	(i) 26 Sept. '04. (ii) 12 Dec. '04.
3	A.S. 263/04	M	58	Squamous cell carcinoma of upper jaw.	Submaxillary glands.	Cicatrices at apex of left lung.	(ii) Fairly nourished.	(i) 22 Nov. '04. (ii) 10 Dec. '04.
4	C.A. 30/04	F	56	Spheroidal cell carcinoma of neck, extending to right lung.	Lymphatic glands, root of lung.	*Lungs:* old tuberculosis both upper lobes; recent tuberculosis right middle and lower lobes.	(ii) Some wasting. Treated by Otto Schmidt's method.	(i) 21 Sept. '03. (ii) 28 Jan. '04.
5	E.W. 42/04	M	84	Squamous cell carcinoma of lip.	Submaxillary and bronchial glands.	Old tuberculosis upper lobe of right lung. Hæmorrhage into ileum. Chronic renal fibrosis Old peritoneal adhesions.	(ii) Great emaciation.	(i) 23 July '03. (ii) 13 Feb. '04.
6	C.V. 128/04	M	61	Squamous cell carcinoma of lip extending to mandible, tongue, palate, and sphenoid bone.	Cervical and submaxillary glands.	Abscess in body of sphenoid bone. Old tuberculosis at apex of right lung.	(ii) Emaciation.	(i) 26 Jan. '04. (ii) 2 June '04.
7	W.C. 148/04	M	62	Squamous cell carcinoma of lip.	Submaxillary lymphatic glands.	... ...	(ii) Extreme emaciation.	(i) 19 Feb. '04. (ii) 26 June '04.

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8	T.H. 199/04	M	67	Squamous cell carcinoma of lip extending to lower jaw.	None.	Gangrene lower lobe of left lung.	(ii) Great emaciation.	(i) 16 March '04. (ii) 21 Sept. '04.
9	G.F. 7/04	M	47	Squamous cell carcinoma of tongue extending to face and cervical muscles.	Cervical glands.	Left kidney the seat of congenital cystic disease. Right kidney hypertrophied and slightly cystic.	(ii) Emaciation.	(i) 29 Oct '03. (ii) 5 Jan. '04. (iii) Partial excision of tongue.
10	T.A. 28/04	M	57	Squamous cell carcinoma of tongue extending to neck.	None.	Aortic cusps calcareous and incompetent. Marked atheroma of pulmonary cusps. Mitral and tricuspid cusps fibrotic. *Lungs:* septic broncho-pneumonia. Rectal polypus.	(ii) Great wasting.	(i) 30 Oct. '03. (ii) 24 Jan. '04.
11	G.P. 39/04	M	58	Squamous cell carcinoma of tongue.	Cervical glands.	Mitral valve fibrotic. Old tuberculosis in upper lobes of both lungs.	(i) Double arterial supply to right kidney. Inferior duodenal and retrocolic fossæ present. (ii) Great emaciation.	(i) 8 Aug. '03. (ii) 12 Feb. '04.
12	W.C. 117/04	M	36	Squamous cell carcinoma of tongue extending to mandible.	Submaxillary and cervical glands.	Cicatrices at apices of both lungs.	(ii) Emaciation.	(i) 22 April '04. (ii) 16 May '04.
13	J.W. 176/04	M	55	Squamous cell carcinoma of tongue.	Submaxillary lymphatic glands on both sides.	Pneumonia of lower lobe of right lung.	(ii) Great emaciation.	(i) 10 Aug. '03. (ii) 29 July '04. (iii) Excision of tongue.
14	J.N. 271/04	M	63	Squamous cell carcinoma of tongue extending to submaxillary region.	None.	Bronchitis and œdema of lungs. Chronic renal fibrosis.	(ii) Extreme emaciation.	(i) 12 Nov. '04. (ii) 17 Dec. '04. (iii) Excision of tongue.
15	A.B. 82/04	M	55	Squamous cell carcinoma of tonsil extending to pharynx.	Tongue, cervical glands.	*Lungs:* broncho-pneumonia.	(ii) Great emaciation.	(i) 17 Nov. '03. (ii) 7 April '04.

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TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
16	W.T. 232/04	M	55	Squamous cell carcinoma of tonsil.	Cervical glands, thyroid body.	Gangrene of upper lobe of right lung. Erysipelas.	(ii) Fairly nourished.	(i) 26 May '04. (ii) 10 Nov. '04.
17	J.K. 244/04	M	63	Squamous cell carcinoma of right tonsil extending to larynx.	Right cervical glands.	Universal adhesion of pericardium. Universal peritoneal adhesions.	(ii) Well nourished.	(i) 15 Nov. '04. (ii) 28 Nov. '04.
18	J.G.S. 45/04	M	61	Squamous cell carcinoma of larynx, invading œsophagus and thyroid body.	Cervical glands.	*Lungs:* broncho-pneumonia. Mitral cusps fibrosed.	(i) Para- and inferior duodenal fossæ. (ii) Fairly nourished.	(i) 7 Jan. '04. (ii) 16 Feb. '04. (iii) Tracheotomy.
19	F.M. 122/04	F	48	Squamous cell carcinoma of larynx extending to œsophagus.	Cervical and infra-tracheal lymphatic glands, lung.	Uterine fibroids. Hæmorrhage into stomach.	(ii) Great emaciation.	(i) 12 May '04. (ii) 28 May '04. (iii) Tracheotomy.
20	J.W. 23/04	M	63	Squamous cell carcinoma of œsophagus extending to trachea.	Cervical glands.	*Lungs:* septic pneumonia with early gangrene.	(ii) Hosp. p.m. 17. Some wasting.	(i) 7 Jan. '04. (ii) 19 Jan. '04.
21	J.S. 58/04	M	62	Squamous cell carcinoma of œsophagus (middle).	None.	*Lungs*; broncho-pneumonia.	(ii) Hosp. p.m. 49. Some emaciation.	(i) 12 Feb. 04. (ii) 7 Mar. '04.
22	W.L. 156/04	M	63	Squamous cell carcinoma of œsophagus (middle) extending to bronchus.	None.	Broncho-pneumonia. Pleural effusion.	(ii) Hosp. p.m. 130. Emaciation.	(i) 6 June '04. (ii) 8 July '04.
23	T.M. 166/04	M	47	Squamous cell carcinoma of œsophagus (middle).	Œsophagus (below primary growth), trachea, lungs.	Septic broncho-pneumonia. Non-malignant adenoma of cheek. Dysenteric ulceration of large bowel.	(ii) Hosp. p.m. 135. Considerable emaciation.	(i) 1 June '04. (ii) 19 July '04.

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24	F.E. 220/04	M	74	Squamous cell carcinoma of œsophagus (middle).	Lungs, thyroid, aorta, trachea, bronchial glands.	... ...	(ii) Emaciation.	(i) 12 Aug '04. (ii) 25 Oct. '04.
25	C.P. 258/04	M	49	Squamous cell carcinoma of œsophagus extending to right bronchus.	None.	... ...	(ii) Hosp. p.m. 233. Great emaciation.	(i) 2 Dec. '04. (ii) 7 Dec. '04.
26	E.H. 273/04	M	43	Squamous cell carcinoma of œsophagus extending to trachea.	Lymphatic glands.	Atheroma of aorta.	(ii) Emaciation.	(i) 6 Oct. '04. (ii) 21 Dec. '04. (iii) Gastrostomy.
27	J.G. 97/04	M	54	Spheroidal cell carcinoma of œsophagus (lower end).	Liver, portal, bronchial, supraclavicular, and iliac glands.	... ...	(ii) Hosp. p.m. 89. Wasting.	(i) 23 March '04. (ii) 29 April '04.
28	M.M. 272/04	F	34	Spheroidal cell carcinoma of stomach (cardiac end).	Liver, both ovaries.	... ...	(ii) Fairly well nourished.	(i) 28 Nov. '04. (ii) 20 Dec. '04. (iii) Double oöphorectomy.
29	M.L. 116/04	F	56	Spheroidal cell carcinoma of middle of stomach.	Liver.	Peritonitis.	(ii) Hosp. p.m. 104. Considerable emaciation.	(i) 22 April '04. (ii) 15 May '04.
30	E.G. 120/04	M	63	Columnar cell carcinoma of middle of stomach.	None.	... ...	... ...	(i) 18 April '04. (ii) 22 May '04.
31	W.B. 80/04	M	50	Spheroidal cell carcinoma of splenic flexure; columnar cell carcinoma of hepatic flexure.	None.	Acute peritonitis.	(ii) Hosp. p.m. 72. Well nourished.	(i) 4 April '04. (ii) 5 April '04. (iii) Short circuiting of intestine.
32	A.B. 31/04	M	43	Columnar cell carcinoma of sigmoid flexure.	None.	... ...	(ii) Hosp. p.m. 29. Great emaciation.	(i) 17 Jan. '04. (ii) 30 Jan. '04.
33	D.S. 266/04	M	50	Columnar cell carcinoma of sigmoid flexure extending to bladder.	Liver, iliac lymphatic glands.	... ...	(ii) Hosp. p.m. 235. Great emaciation.	(i) 5 Nov. '04. (ii) 12 Nov. '04.

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TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
34	M.A.S. 34/04	F	56	Columnar cell carcinoma of sigmoid flexure.	None.	Stercoral ulcer in cæcum.	(ii) Hosp. p.m. 31. No marked emaciation.	(i) 1 Feb. '04. (ii) 2 Feb. '04. (iii) Colotomy.
35	R.M. 66/04	M	52	Columnar cell carcinoma of rectum.	Liver, lungs.	Renal fibrosis.	(ii) Well nourished.	(i) 15 Dec. '03, (ii) 12 March '04.
36	E.J. 93/04	M	61	Columnar cell carcinoma of rectum.	Liver.*	... ...	(ii) Hosp. p.m. 85. Slight wasting. Treated by Otto Schmidt's method.	(i) 10 March '04. (ii) 22 April '04. (iii) Colotomy.
37	W.W. 149/04	M	61	Columnar cell carcinoma of rectum.	Liver.	General peritonitis.	(ii) Hosp. p.m. 125. Fairly nourished.	(i) 27 May '04. (ii) 30 June '04. (iii) (*a*) Left lumbar colotomy. (*b*) Excision of rectum.
38	F.S. 179/04	M	67	Columnar cell carcinoma of rectum invading sacrum.	None.	Atheroma of aortic cusps: cardiac hypertrophy.	(ii) Great emaciation.	(i) 28 April '04. (ii) 5 Aug. '04.
39	J.N. 195/04	M	28	Columnar cell carcinoma of rectum extending to bladder and prostate.	Liver, inguinal glands, omentum, mesentery, and peritoneum generally. Abdominal lymphatic glands.*	Matting together of intestines.	(ii) Great emaciation. Ascites.	(i) 8 April '04. (ii) 17 Sept. '04. (iii) Inguinal colotomy.
40	R.W. 158/04	F	65	Transitional cell carcinoma of rectum.	Left pleura, bronchial glands.	Chronic renal fibrosis.	(ii) Great emaciation.	(i) 6 June '03. (ii) 11 July '04, (iii) Inguinal colotomy.

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41	C.C. 177/04	M	64	Spheroidal cell carcinoma of liver.	None.	Calcification at apex of right lung. Hæmorrhagic ascites.	(ii) Hosp. p.m. 146. Wasting. No jaundice.	(i) 19 July '04. (ii) 2 Aug. '04.
42	H.W. 180/04	F	59	Spheroidal cell carcinoma of liver.	Intestine, peritoneum, ovarian cyst.	Multilocular ovarian cyst. Ascites.	(ii) Hosp. p.m. 147. Legs œdematous. No jaundice. Not emaciated.	(i) 28 July '04. (ii) 4 Aug. '04.
43	T.S. 270/04	M	61	Columnar cell carcinoma of liver (? Endothelioma).	None.	Ascites. Jaundice. Cirrhosis of liver.	(ii) Well nourished.	(i) 28 Nov. '04. (ii) 19 Dec. '04.
44	A.McL. 211/04	F	50	Columnar cell carcinoma of cystic duct.	Liver, omentum, ovaries.	... ...	(ii) Hosp. p.m. 195. Great emaciation. Jaundice. Gall stones. Ascites.	(i) 22 Sept. '04. (ii) 11 Oct. '04.
45	A.L. 92/04	F	48	Spheroidal cell (colloid) carcinoma of pancreas.	Omentum, suprarenal, lymphatic glands, thoracic duct.*	... ...	(ii) Hosp. p.m. 84. Fairly nourished. Jaundice.	(i) 2 April '04. (ii) 20 April '04.
46	R. de V. 173/04	F	65	Spheroidal cell carcinoma of pancreas.	Liver.	... ...	(ii) Hosp. p.m. 140. Emaciation. Jaundice.	(i) 16 June '04. (ii) 24 July '04.
47	S.D. 102/04	M	31	Squamous cell carcinoma of urinary bladder.	Pelvic glands, prostate.	Calculi in Wirsung's duct. Tuberculosis of both lungs with vomicæ. Prostate cystic.	(ii) Hosp. p.m. 90. Wasting. Diabetes.	(i) 21 April '04. (ii) 2 May '04.
48	R.G. 249/04	M	64	Spheroidal cell carcinoma of prostate invading bladder.	None.	Calcification of pleural adhesions.	(ii) Hosp. p.m. 228. Fairly nourished.	(i) 18 Nov. '04. (ii) 30 Nov. '04. (iii) Exploratory incision.
49	H.L. 94/04	M	53	Squamous cell carcinoma of scrotum.	Inguinal and femoral lymphatic glands, penis.	*Lungs:* cicatrization at both apices. Atheroma of aorta. Optic atrophy.	(i) Meckel's diverticulum.	(i) 17 Feb. '04. (ii) 27 April '04.
50	E.N. 233/04	M	70	Squamous cell carcinoma of inguinal region (? scrotum).	... ...	... ...	(ii) Fairly nourished.	(i) 30 Aug. '04. (ii) 11 Nov. '04.

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TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
51	R.B. 163/04	F	45	Spheroidal cell carcinoma of body of uterus.	Peritoneum.	... ...	(ii) Fairly nourished. Partial examination only.	(i) 27 Feb. '04. (ii) 16 July '04. (iii) Lumbar colotomy (abortive).
52	E.N. 200/04	F	76	Spheroidal cell carcinoma of uterus.	None.	Chronic renal fibrosis with some dilatation of ureters. Sloughing of upper part of vagina.	(ii) Fairly nourished.	(i) 15 July '04. (ii) 22 Sept. '04.
53	E.C. 276/04	F	53	Spheroidal cell carcinoma of uterus.	Liver,* aortic lymph glands.	Dilated œsophageal veins. Hæmatemesis.	(ii) No wasting.	(i) 23 Dec. '04. (ii) 25 Dec. '04.
54	M.E. 277/04	F	43	Spheroidal cell carcinoma (recurrent) of uterus.	Peritoneum.	Intestinal obstruction. Stercoral ulcers. Peritonitis.	(ii) Fairly nourished.	(i) 12 Dec. '04. (ii) 30 Dec. '04.
55	E.S. 46/04	F	62	Columnar cell carcinoma (becoming transitional) of body of uterus.	Iliac glands, omentum, right ovary.	Great atheroma of aorta. Old peritoneal adhesions in pelvis. A litre of fluid in right pleural cavity.	(ii) Slight wasting.	(i) 25 Jan. '04. (ii) 18 Feb. '04.
56	S.B. 182/04	F	55	Columnar cell carcinoma of uterus.	Liver, spine, perirenal tissue.	Left kidney hydronephrotic. Right kidney contains uric acid gravel.	(ii) Great emaciation.	(i) 19 Feb. '04. (ii) 10 Aug. '04. (iii) Hysterectomy.
57	M.P. 234/04	F	58	Columnar cell carcinoma of body of uterus becoming transitional	Peritoneum, liver, lymphatic gland.	Ascites. Fibro-myomata of uterus. Thrombosis of pampiniform and left internal iliac veins.	(ii) Hosp. p.m. 217. Well nourished.	(i) 19 Sept. '04. (ii) 14 Nov. '04. (iii) Laparotomy.
58	F.E.K. 245/04	F	38	Spheroidal cell carcinoma of cervix uteri.	Colon, aortic lymphatic glands.	... ...	(ii) Fairly nourished.	(i) 25 April '04. (ii) 30 Nov. '04.

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59	S.W. 18/04	F	44	Columnar cell carcinoma of cervix uteri.	None.	... ...	(ii) Hosp. p.m. 16. Very obese.	(i) 31 Dec. '03. (ii) 16 Jan. '04. (iii) Hysterectomy.
60	E.P. 38/04	F	57	Columnar cell carcinoma of cervix uteri.	Iliac lymphatic glands.	Atheroma of aorta. Ureters dilated. Marked atrophic fibrosis of liver. No gallstones or nodules of growth.	(ii) Fairly nourished. Deeply jaundiced. Occlusion of left internal iliac artery.	(i) 9 Dec. '02. (ii) 10 Feb. '04.
61	M.S. 47/04	F	39	Columnar cell carcinoma (becoming transitional) of cervix uteri.	Right inguinal glands.*	Slight hydronephrosis. Cystitis.	(ii) Well nourished. Gallstones.	(i) 18 Jan. '04. (ii) 20 Feb. '04. (iii) Amputation of cervix.
62	M.A.W. 213/04	F	45	Columnar cell carcinoma of cervix uteri.	Ovary, broad ligament, lumbar glands.	Double hydronephrosis. Fibro-myoma of uterus.	(ii) Fairly well nourished. Anæmia.	(i) 18 July '04. (ii) 14 Oct. '04.
63	E.P. 19/04	F	46	Squamous cell carcinoma of cervix uteri extending to bladder.	Iliac lymphatic glands.*	Vesico-vaginal fistula.	(ii) Emaciation.	(i) 19 Feb. '03. (ii) 18 Jan. '04.
64	S.R. 24/04	F	49	Squamous cell carcinoma of cervix uteri.	Liver, pelvic lymph glands.	*Kidneys:* left hydronephrotic; right, pyonephrotic. Ureters dilated. Calcified fibroma at fundus of uterus. Ovaries cystic.	(i) Ossified stylo-hyoid ligament. (ii) Fairly well nourished.	(i) 12 Oct. '03. (ii) 21 Jan. '04.
65	E.B. 43/04	F	56	Squamous cell carcinoma of cervix uteri.	Liver.	Old tuberculosis upper lobe of left lung. Double hydronephrosis.	(ii) Fairly nourished. Vesico-vaginal fistula.	(i) 4 March '03. (ii) 14 Feb. '04.
66	J.P. 44/04	F	43	Squamous cell carcinoma of cervix uteri.	Inguinal, iliac, and aortic lymphatic glands.	*Lungs:* broncho-pneumonia. Double hydronephrosis. Recent peritonitis. Adenoma of thyroid body.	(ii) Fairly nourished.	(i) 20 Jan. '04. (ii) 17 Feb. '04.

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TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
67	S.W. 55/04	F	67	Squamous cell carcinoma of cervix uteri extending to bladder.	Iliac lymphatic glands.	*Lungs:* broncho-pneumonia. *Kidneys:* Right, 7 oz.; left, 1 oz. fibrotic. Adenoma of right adrenal. Vesico-vaginal fistula.	(ii) Well nourished.	(i) 16 Jan. '01. (ii) 2 March '04.
68	D.A. 77/04	F	33	Squamous cell carcinoma of cervix uteri.	Lumbar lymph glands.	Aortic incompetence. Double hydronephrosis. Syphilitic ulcers of arm, leg, and foot. Vesico-vaginal fistula.	(i) Four cusps in pulmonary valve. (ii) Great emaciation.	(i) 12 Feb. '04. (ii) 28 March '04.
69	E.C. 95/04	F	48	Squamous cell carcinoma of cervix uteri extending into left broad ligament and peritoneal cavity.	Capsule of spleen.	Extensive atheroma of aorta. Cicatrization apex of right lung. Great dilatation of stomach. Slight hydronephrosis.	(ii) Slight wasting.	(i) 18 March '04. (ii) 28 April '04.
70	S.A.C. 108/04	F	50	Squamous cell carcinoma of cervix. Cystadenoma of ovary.	Lymphatic glands, left adrenals and kidney, spleen, liver, lungs. Thoracic duct.	Cicatrization at apices of both lungs. Hour-glass contraction of stomach. Peritonitis. Hydronephrosis.	(ii) Great emaciation.	(i) 20 April '04. (ii) 8 May '04.
71	M.A.B. 114/04	F	75	Squamous cell carcinoma of cervix extending to bladder.	None.	Umbilical omental hernia. Bronchitis.	(ii) Slight wasting.	(i) 22 March '04. (ii) 12 May '04.
72	C.M. 123/04	F	43	Squamous cell carcinoma (? endothelioma) of cervix.	Liver.	Hydronephrosis. General peritonitis.	(ii) Great emaciation. Vesico - vaginal fistula.	(i) 22 Jan. '04. (ii) 30 May '04.

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73	R.W. 141/04	F	31	Squamous cell carcinoma of cervix extending to bladder and intestine.	None.	Perforation of intestine. General peritonitis.	(ii) Extreme wasting.	(i) 23 July '03. (ii) 15 June '04.
74	M.R. 155/04	F	40	Squamous cell carcinoma of cervix.	Mesentery, abdominal glands, spleen.	General peritonitis.	(ii) Extreme emaciation.	(i) 30 April '04. (ii) 8 July '04. (iii) Laparotomy. Inguinal colotomy.
75	L.C.C. 161/04	F	56	Squamous cell carcinoma of cervix.	None.	Cicatrization at apices of both lungs. Advanced mitral stenosis. Pus in Douglas's pouch.	(ii) Much subcutaneous fat.	(i) 12 July '04. (ii) 13 July '04.
76	E.D. 162/04	F	57	Squamous cell carcinoma of cervix uteri.	Rectum.	Pyonephrosis.	(ii) Great emaciation. Vagino-vesical fistula.	(i) 7 May '04. (ii) 15 July '04.
77	C.B. 164/04	F	45	Squamous cell carcinoma of cervix uteri.	None.	Consecutive nephritis.	(ii) Great emaciation. Ileo-vaginal fistula. Vesico-vaginal fistula.	(i) 9 May '04. (ii) 17 July '04. (iii) Vaginal hysterectomy.
78	S.E.W. 167/04	F	51	Squamous cell carcinoma of cervix uteri.	Sigmoid flexure, Fallopian tube, liver.	Pyonephrosis. Local peritonitis.	(ii) Great wasting. Recto-vaginal and vesico-vaginal fistulæ.	(i) 1 June '04. (ii) 19 June '04.
79	M.A.R. 168/04	F	53	Squamous cell carcinoma of cervix uteri.	Lumbar glands.	Old peritonitic adhesions. Scar in appendix. Consecutive nephritis and pyonephrosis.	(ii) Well nourished. Vesico-vaginal fistula.	(i) 19 July '04. (ii) 22 July '04.
80	E.Z. 190/04	F	46	Squamous cell carcinoma of cervix invading bones of pelvis and bladder.	None.	Cicatrices at apices of both lungs. Peritonitic adhesions.	(ii) Emaciation.	(i) 15 Aug. '04. (ii) 1 Sept. '04.
81	C.C. 191/04	F	60	Squamous cell carcinoma of cervix extending to rectum and bladder.	None.	Cicatrices at apices of both lungs. Double hydronephrosis: more marked on right side.	(ii) Great emaciation and anæmia.	(i) 17 May '04. (ii) 11 Sept. '04.

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TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
82	M.A.M. 194/04	F	57	Squamous cell carcinoma of cervix extending to ovaries and bladder.	None.	Cicatrices at apices of both lungs.	(ii) Wasting.	(i) 19 Jan. '04. (ii) 17 Sept. '04. (iii) Amputation of cervix : colotomy.
83	L.P. 217/04	F	39	Squamous cell carcinoma of cervix.	Vagina, ovaries, broad ligaments, lymphatic glands, lungs.	Caseous nodule at apex of right lung; cicatrix at apex of left lung. Ileo-vaginal fistula. Suppuration about left sacro-iliac synchondrosis, and also abscess extending from last rib to iliac fossa on right side.	(ii) Great emaciation and anæmia.	(i) 17 Feb. '04. (ii) 21 Oct. '04.
84	N.P. 240/04	F	31	Squamous cell carcinoma of cervix uteri.	Aortic glands, scalp.	... ...	(ii) Emaciated.	(i) 19 Sept. '04. (ii) 19 Nov. '04.
85	M.S. 264/04	F	37	Squamous cell carcinoma of cervix.	Pelvic lymphatic glands.	Double hydronephrosis.	(ii) Great emaciation and anæmia.	(i) 16 Sept. '04. (ii) 11 Dec. '04.
86	M.M. 275/04	F	39	Squamous cell carcinoma of cervix extending to fundus uteri.	Iliac lymphatic glands.	Abscess cavity in pelvis.	(ii) Some wasting.	(i) 11 May '04. (ii) 27 Dec. '04.
87	J.W. 105/04	F	61	Squamous cell carcinoma of vagina.	Iliac lymphatic glands, liver.	Enlarged inguinal glands (non-malignant). Old tuberculous focus at apex of left lung. Tænia mediocanellata. Calcified splenic artery.	(ii) Extreme emaciation.	(i) 18 April '04. (ii) 5 May '04.
88	E.F. 242/04	F	39	Squamous cell carcinoma of vagina.	Liver, inguinal glands.	Fibro-myoma of kidney.	(ii) Wasting.	(i) 10 Oct. '04. (ii) 24 Nov. '04.

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89	A.McC. 25/04	F	67	Carcinoma of vulva.†	Inguinal glands.†	*Heart:* calcification of cusps of mitral valve. Peritonitis. *Liver:* multilobular fibrosis.	(i) Inferior duodenal and retrocæcal fossæ. (ii) Fairly well nourished.	(i) 26 Dec. '03. (ii) 20 Jan. '04.
90	M.A.L. 2/04	F	46	Spheroidal cell carcinoma both ovaries extending to uterus and bladder.	Liver, peritoneum, aortic and mesenteric glands, pleuræ.*	*Lungs:* double pneumonia. *Pleuræ:* sanguineous fluid in each pleural cavity. *Kidneys:* chronic fibrosis.	(ii) Great emaciation.	(i) 17 Dec. '03. (ii) 2 Jan. '04. (iii) Laparotomy.
91	S.F. 33/04	F	51	Papilliferous cystadenoma of ovary.	Liver, peritoneum, small intestine, abdominal lymphatic glands.*	Universally adherent pericardium. Fluid in both pleural cavities. Three and a half litres of thick purulent fluid in abdominal cavity.	(ii) Great emaciation.	(i) 22 Sept. '02. (ii) 2 Feb. '04. (iii) Laparotomy.
92	A.M. 131/04	F	54	Cystadenoma of both ovaries. Columnar cell carcinoma of colon (splenic flexure).	Liver, appendix.	General peritonitis. Perforation of cæcum. Uterine fibroids.	(ii) Hosp. p.m. 115 Some wasting.	(i) 2 June '04. (ii) 3 June '04.
93	E.M. 221/04	F	59	Papilliferous cystadenoma of ovaries extneding to adjacent parts.	Peritoneum, spleen, uterus, liver, pelvic lumbar aortic and bronchial glands.	Abdominal organs matted together by adhesions.	(ii) Extreme emaciation. Anæmia. Ascites. Pleural effusions.	(i) 2 Feb. '04 (ii) 25 Oct. '04.
94	S.deS. 257/04	F	56	Papilliferous cystadenoma of ovaries.	Peritoneum.	Pleural effusion and collapse of left lung. Ascites. Peritoneal adhesions. Extensive atheroma of aorta.	(ii) No emaciation.	(i) 21 Nov. '04. (ii) 6 Dec. '04. (iii) Laparotomy.
95	S.H. 253/04	F	66	Spheroidal cell carcinoma of both breasts.	Axillary glands both sides, liver.	Adherent pericardium. Gallstones. Dilatation of gall bladder. Senile fibrosis of kidneys.	(ii) Well nourished.	(i) 30 July '04. (ii) 3 Dec. '04. (iii) Amputation of left breast.

† Included on strong macroscopic grounds; only inflammatory changes found microscopically.

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TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
96	H.A. 267/04	F	58	Spheroidal cell carcinoma both breasts extending to pleuræ and axilla.	None.	Œdema of right arm. A few small uterine fibroids.	(ii) Fairly nourished.	(i) 7 May '02. (ii) 15 Dec. '04.
97	H.M. 1/04	F	42	Spheroidal cell carcinoma of right breast.	Liver, sixth to twelfth dorsal vertebræ.	*Lungs:* old tuberculosis right upper lobe. *Kidneys:* chronic fibrosis. *Bladder:* cystitis. *Ovaries:* left multilocular cyst.	(ii) Well nourished.	(i) 14 Dec. '03. (ii) 1 Jan. '04.
98	A.R. 21/04	F	50	Spheroidal cell carcinoma of right breast.	Right axillary lymphatic glands, left breast, liver, lungs, uterus, kidneys.	Mitral stenosis. Fatty degeneration of cardiac muscle. Sanguineous fluid in both pleural cavities.	(ii) Well nourished. Treated by Otto Schmidt's method.	(i) 6 Nov. '03. (ii) 19 Jan. '04.
99	A.W. 64/04	F	47	Spheroidal cell carcinoma of right breast.	Liver, lungs, kidney, left ovary.	*Lungs:* broncho-pneumonia. Fibro-myoma of uterus.	(i) Foramen ovale patent. (ii) Body thin.	(i) 12 Jan. '04. (ii) 11 March '04.
100	A.W. 69/04	F	63	Spheroidal cell carcinoma of right breast.	Axillary tissues including lymph glands.	Recent vegetations on mitral valve. *Lungs:* broncho-pneumonia. Cystic adenomata of thyroid. Fibroma in gastric wall. Three polypi in large intestine.	(i) Foramen ovale patent. (ii) Well nourished. Great œdema of right arm.	(i) 8 June '03. (ii) 17 March '04.
101	E.L. 109/04	F	66	Spheroidal cell carcinoma of right breast.	Axillary and supra-clavicular glands, liver, bronchus, pleura, ribs, left breast.	Right sanguineous pleural effusion. Extensive atheroma of aorta.	(ii) No emaciation. Œdema of right arm.	(i) 4 Jan. '04. (ii) 7 May '04.

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102	T.M. 144/04	F	60	Spheroidal cell carcinoma of right breast.	Pericardium. Axillary tissues.	Old tuberculosis at apices of both lungs. Pericardial effusion.	(ii) Well nourished. Œdema of right arm.	(i) 15 Dec. '03. (ii) 20 June '04.
103	M.B. 219/04	F	37	Spheroidal cell carcinoma of right breast.	Lung and pleura, liver, clavicle, left ovary, right adrenal, spleen, lymphatic glands.	Calcareous nodule at apex of right lung.	(ii) Great wasting. Pleural effusion (right). Weight of spleen 34 oz.	(i) 23 March '04. (ii) 25 Oct. '04. (iii) Amputation of breast.
104	F.B. 269/04	F	74	Spheroidal cell carcinoma of right breast.	None.	Chronic renal fibrosis.	(ii) Marked emaciation. Treated by Otto Schmidt's method.	(i) 26 March '01. (ii) 17 Dec. '04.
105	E.S. 274/04	F	73	Spheroidal cell carcinoma of right breast extending to axilla.	None.	Cicatrices at apices of both lungs.	(ii) Some wasting. Œdema of right arm.	(i) 13 Nov. '04. (ii) 23 Dec. '04.
106	M.A.McN. 17/04	F	58	Spheroidal cell carcinoma of left breast.	Pancreas, thyroid body extending to trachea and œsophagus, mesenteric glands, small intestine, uterus.	*Brain:* cavities filled with granular débris in right temporal lobe and in positions of anterior cornua of both lateral ventricles. *Lungs:* broncho-pneumonia. Uterine fibro-myomata.	(ii) Well nourished.	(i) 11 April '03. (ii) 16 Jan. '04.
107	F.H. 26/04	F	42	Spheroidal cell carcinoma of left breast.	Lung, liver, pancreas, axillary glands.*	... ...	(ii) Hosp. p.m. 21. Emaciation.	(i) 21 Dec. '03. (ii) 20 Jan. '04.
108	B.C. 72/04	F	37	Spheroidal cell carcinoma of left breast.	Right breast, axillary and lumbar glands, thyroid, liver, pleura, lumbar vertebra.	Chronic renal fibrosis. Pleural effusion on left side.	(ii) Body thin.	(i) 1 Feb. '04. (ii) 21 March '04.
109	N.J. 81/04	F	42	Spheroidal cell carcinoma of left breast.	Axillary, lumbar, bronchial glands, skin, lung, kidney, liver, thoracic duct.	... ...	(ii) Hosp. p.m. 144 Great emaciation. Jaundice.	(i) 28 March '04. (ii) 28 July '04. (iii) Amputation of breast.

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TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
110	S.A.K. 89/04	F	39	Spheroidal cell carcinoma of left breast.	Liver, lung, vertebræ, ileum, portal,* iliac,* and aortic glands.	... ...	(ii) Emaciation. Jaundice.	(i) 25 Sept. '03. (ii) 18 April '04. (iii) Amputation of breast.
111	E.U. 175/04	F	64	Spheroidal cell carcinoma of left breast.	Axillary, cervical, bronchial, mesenteric and lumbar glands, lumbar vertebræ, liver, lungs, left suprarenal, spleen, femur.	Hæmorrhagic pleural effusions. Fracture of right femur.	(ii) Wasting.	(i) 28 March '04. (ii) 27 July '04. (iii) Amputation of breast.
112	C.E.H. 188/04	F	43	Spheroidal cell carcinoma (? endothelioma) of left breast.	Lymphatic glands, skin, cerebrum, pons and cerebellum, right kidney, lungs, pancreas, left ovary, intestine,* liver,* suprarenals.*	Complete atrophy of left kidney.	(ii) Emaciation.	(i) 20 Aug. '04. (ii) 29 Aug. '04.
113	E.C. 206/04	F	73	Spheroidal cell carcinoma of left breast.	Right breast, right and left axillary, bronchial, supra-clavicular, and lumbar glands, liver, skin, rib.	Atheroma of aorta.	(ii) Great emaciation. Great œdema of right arm.	(i) 17 June '04. (ii) 4 Oct. '04.
114	J.T. 225/04	F	40	Spheroidal cell carcinoma of left breast.	Right breast, ribs, left lung, liver, uterus, ovary, axillary, cervical, portal, bronchial, and lumbar glands.	Fibro-myomata of uterus.	(ii) Emaciation.	(i) 3 Sept. '04. (ii) 1 Nov. '04.

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SARCOMATA.

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
1	M.A.C. 250/04	F	61	Mixed cell sarcoma of left breast extending to ribs, axilla, and lung.	None.	Great œdema of left arm.	(ii) Well nourished.	(i) 2 Sept. '03. (ii) 2 Dec. '04.
2	T.M. 252/04	M	50	Small round cell sarcoma of bronchus.	Bronchial and a few anterior mediastinal glands.	Great stenosis of mitral valve. Right pleural effusion.	(ii) Hosp. p.m. 231. No emaciation.	(i) 2 Dec. '04. (ii) 4 Dec. '04.
3	R.G. 14/04	F	3½	Mixed cell sarcoma of bronchial glands.	Cervical, mediastinal, œsophageal and mesenteric glands, lung,* liver,* spleen.*	... ...	(ii) Emaciation.	(i) 27 Aug. '03. (ii) 13 Jan. '04.
4	P.K. 22/04	M	64	Mixed cell sarcoma of right kidney (cystic and containing 1150 cc. of fluid).	None.	... ...	(ii) Hosp. p.m. 18. Fairly well nourished.	(i) 19 Nov. '03. (ii) 19 Jan. '04.
5	R.A.C. 227/04	F	54	Spindle cell sarcoma of stomach.	Ovary.	... ...	(ii) Hosp. p.m. 211. Extreme emaciation.	(i) 13 Oct. '04. (ii) 5 Nov. '04.
6	A.P. 135/04	M	52	Mixed cell sarcoma of stomach (middle).	None.	... ...	(ii) Hosp. p.m. 119. Well nourished.	(i) 9 May '04. (ii) 9 June '04.
7	E.L. 196/04	F	34	Spindle cell sarcoma (leiomyosarcoma) of uterus.	None.	Great anæmia of all organs.	(ii) Body thin.	(i) 10 Sept. '04. (ii) 15 Sept. '04.

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TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnormalities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
8	L.M. 153/04	F	62	Mixed cell sarcoma of ovary.	Rectum, sigmoid flexure, bladder.	General peritonitis.	(ii) Hosp. p.m. 127. Thin body.	(i) 5 May '04. (ii) 4 July '04. (iii) Laparotomy.
9	S.R. 186/04	F	55	Spindle cell sarcoma of thyroid body.	None.	... ...	(i) Greatly enlarged thymus. (ii) Hosp. p.m. 163. Emaciation. Death under anæsthesia.	(i) 2 Aug. '04. (ii) 27 Aug. '04.
10	M.V. 207/04	F	21	Small round cell sarcoma of lower jaw.	Lung, tongue, adrenals, lymphatic glands.	... ...	(ii) Thin body. Great anæmia.	(i) 12 July '04. (ii) 5 Oct. '04.
11	M.A.T. 145/04	F	44	Melanotic sarcoma of skin of thigh.	Dura mater, brain, pleura, lungs, pericardium, heart, thyroid, liver, pancreas, kidneys, adrenals, peritoneum, lymphatic glands, right breast,* gall-bladder, skin.	Fibro-adenoma of left breast.	(i) Numerous pigmented moles and warts. (ii) Hosp. p.m. 122. Well nourished.	(i) 10 May '04. (ii) 20 June '04.
12	D.B. 223/04	M	24	Melanotic sarcoma right eyelid (mixed cell).	Left frontal lobe of brain.	... ...	(ii) Fairly nourished.	(i) 28 Aug. '04. (ii) 31 Oct. '04. (iii) Excision of primary growth 1897. Removal of lymphatic glands in neck 1904.

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13	J.D. 0	M	50	Melanotic sarcoma of skin of shoulder (mixed cell and alveolar).	Axilliary cœliac and lumbar glands, right pleura, left rib.	60 oz. right pleural effusion. Infarcts of liver.	(ii) Well nourished.	(i) 31 Oct. '04. (ii) 1 Nov. '04. (iii) Removal of primary growth.
14	B.S. 226/04	M	53	Spindle cell sarcoma of urinary bladder.	Left kidney.	Atheroma of aorta. Cicatricial fibrosis at apex of right lung. Pyonephrosis.	(i) Abnormal arrangement of duodenum. (ii) Body thin.	(i) 24 Aug. '04. (ii) 6 Nov. '04. (iii) Suprapubic operation.
15	M.G. 85/04	F	63	Endothelioma of colon (hepatic and splenic flexures).	Ovary, suprarenal, lymphatic glands.	... ...	(ii) Hosp. p.m. 77. Slight wasting.	(i) 8 April '04. (ii) 12 April '04.
16	A.P. 121/04	F	27	Endothelioma of peritoneum.	Abdominal lymphatic glands, ovary.	Recent abortion.	(ii) Hosp. p.m. 108. Considerable emaciation.	(i) 18 April '04. (ii) 22 May '04.
17	L.L. 193/04	F	66	Endothelioma (lymphatic type) of right breast extending to ribs.	None.	Great atheroma of aorta.	(ii) Wasting.	(i) 30 April '04. (ii) 14 Sept. '04.
18	L.C. 251/04	F	53	Endothelioma (lymphatic type) of upper jaw extending to sphenoid bone and orbit.	Dura mater.	Pleural adhesions. Bronchitis.	(ii) Extreme emaciation.	(i) 29 July '04. (ii) 4 Dec. 04.

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"CANCER AGES": A STATISTICAL STUDY BASED ON THE CANCER RECORDS OF THE MIDDLESEX HOSPITAL.

By W. S. LAZARUS-BARLOW, M.D., F.R.C.P.

In compiling a statistical account of the ages of the cancerous patients that have been admitted to the Middlesex Hospital since its earliest records in 1746 to the end of 1904, it is necessary to bear in mind the actual character of the figures that are here presented.

It is clear that the age of "incidence" or of "occurrence" of cancer (using those terms in their strict etymological sense) is not under consideration. For, firstly, the records do not give information in all cases upon the length of time during which the growth had existed previous to admission of the patient, and, secondly, in a very large proportion of cases in which information is given, if not in all, the only ground for the information is the statement of the patient.

It is equally clear that the age at death is not in all cases under consideration. In a fair proportion of the cases the patients underwent operation and left the hospital; nor is there any means of ascertaining their duration of life afterwards. In the case of those patients, however, who died soon after admission the age given in the records practically coincides with the age at death. Where a patient, on the contrary, remained in hospital one or more years after admission, the records are usually silent as to whether the age given is that on admission or that at time of death.

Upon the whole, therefore, the ages dealt with in the following pages are those of the patients at the time when they first came under observation, and this is true even in those instances in which there were re-admissions. Assuming

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that patients suffering from cancer do not usually delay seeking advice after they recognise that something is wrong, it may perhaps be held that the figures given are approximately those at which the new growth makes its existence known to the patient.

In dealing with records that reach back to the first half of the eighteenth century it is clearly impossible to use the word "carcinoma," however probable it may appear that the cases in question were really of that nature. Over the later years, in which microscopic examinations were made, use of the word would be justifiable. But although the methods of selecting the cases were very stringent, being those described in detail in a former paper,* and although there is a high probability that cases of other than carcinomatous nature constitute only a small percentage of error, yet it has been thought advisable to include all cases under the general name of "cancer." In the same way it has not been thought advisable to limit unduly the word "age." Hence the expression "cancer ages" fairly covers the subject matter of the following paragraphs.

In compiling the tables cases were separated into classes according to the situation of the primary growth. In certain instances little or no difficulty was encountered. Malignant growths of the stomach, colon, or rectum were easily separable. But in the case of the region from lips to pharynx some difficulty was experienced. This was not entirely obviated by dividing the cases into (*a*) lip, (*b*) tongue, (*c*) mouth, for in an advanced case it was often difficult to decide the exact point of onset.

With regard to the liver much difficulty and uncertainty lies in the way of separating primary from secondary growths from examination of the records. The method of dealing with this difficulty is referred to in the appropriate place. The same difficulty is felt in large measure in connection with "cancer of the bladder" in females and "cancer of the larynx" in both sexes; in the first instance because of the difficulty of determining whether the uterus, vagina or vulva was not primarily involved, and

* Arch. Middlesex Hosp., Vol. iii., p. 130.

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in the second because of the uncertainty whether the growth was not primarily œsophageal.

From these causes the value of the results obtained in the various classes of case detailed below is not equal. An even greater cause of difference in the value of the results depends upon the differences in the numbers of cases entering into the various categories. The value of an average derived from 40 cases (vagina) cannot be so great as one derived from 1,971 (uterus). The entire series of cases used in the present investigation is shown in Table I.

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TABLE I.

TABLE SHOWING THE NUMBER OF CASES OF CANCER IN VARIOUS QUINQUENNIAL AGE-PERIODS, AND IN REFERENCE TO THE SITE OF PRIMARY GROWTH.

AGE.	ALIMENTARY TRACT.																Glands accessory to Alimentary Tract.				GENERATIVE TRACT.						OTHER SITES.											
	Lip.		Tongue.		Other parts of Mouth.		Œsophagus.		Stomach.		Colon.		Rectum.		Anus.		Liver.		Pancreas.		Penis.	Scrotum.	Prostate.	Uterus.	Vagina.	Vulva.	Bladder.		Breast.		Skin.		Rodent Cancer.		Larynx.	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	M.	M.	F.	F.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
15—19...	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
20—24...	—	—	1	—	1	—	—	—	—	1	—	—	4	1	—	—	—	—	—	—	2	—	—	8	1	—	—	—	2	—	—	—	—	—	—	—
25—29...	1	—	0	2	1	—	3	1	5	1	1	1	5	11	—	—	—	—	—	—	1	—	—	73	—	—	—	—	17	—	—	1	—	—	—	—
30—34...	0	—	0	2	1	2	2	3	4	5	0	1	10	11	—	—	—	—	—	—	3	3	—	146	2	1	—	—	71	—	2	4	1	—	—	—
35—39...	10	—	13	7	11	3	2	1	8	10	3	2	12	17	—	—	7	4	1	—	6	3	—	278	3	3	—	—	145	2	0	2	4	1	—	—
40—44...	15	—	46	6	26	3	11	4	18	14	7	12	30	21	—	—	6	12	1	2	7	9	—	359	8	4	—	2	6	261	3	5	7	2	—	—
45—49...	27	—	76	13	34	3	24	4	32	15	11	7	26	23	—	1	9	8	0	3	8	5	—	361	8	6	3	1	2	298	3	6	13	14	6	1
50—54...	33	2	98	12	44	6	34	8	46	18	18	10	42	43	1	0	6	5	3	4	9	9	—	310	6	10	7	2	4	286	4	3	17	11	6	3
55—59...	33	2	65	9	52	8	52	3	36	18	10	13	35	32	0	0	11	8	3	2	4	5	1	190	1	14	2	7	3	251	3	2	15	6	4	0
60—64...	36	0	62	5	55	6	43	3	21	26	9	11	44	38	3	2	16	19	3	3	8	1	2	145	6	17	2	5	2	217	12	8	22	9	5	1
65—69...	22	2	34	7	16	6	16	2	13	6	14	6	36	16	0	1	4	9	3	3	7	0	2	66	4	15	7	3	1	119	7	6	16	18	2	—
70—74...	28	1	26	6	18	4	6	1	8	2	2	1	16	7	1	1	2	5	1	—	5	1	5	22	1	6	3	2	1	60	3	3	13	11	2	—
75—79...	13	—	5	1	3	3	1	—	1	2	3	1	5	4	—	1	—	—	—	—	2	—	—	13	—	7	1	1	—	25	4	2	7	6	—	—
80—84...	8	—	2	—	1	—	1	—	—	—	—	—	1	—	—	1	—	—	—	—	—	—	—	—	—	3	—	—	—	4	2	—	1	1	—	—
85—89...	—	—	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	—	—	1	4	—	—	1	—	—	—
Totals...	226	7	429	70	264	44	195	30	192	118	78	65	267	224	5	7	61	70	15	17	62	36	10	1,971	40	88	25	23	20	1,760	43	37	119	83	26	5

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I.—THE ALIMENTARY TRACT.

Dealing with the entire tract and comparing males with females, the two most striking points are 1° the far greater prevalence of cancer in this region in males, and 2° the later age at which males are affected.

TABLE II.

Table showing Mean, Minimum, and Maximum Ages observed at the Middlesex Hospital in cases of Cancer of the Alimentary Tract.

(Figures for Females are printed in heavy type.)

Site of Primary Growth.	Number of Cases.	Mean Age in Years.	Minimum Age in Years.	Maximum Age in Years.
Lip	226	58·668	29	84
	7	**60·714**	**51**	**73**
Tongue	429	54·587	24	85
	70	**52·171**	**28**	**75**
Other parts of Mouth ...	264	55·314	24	85
	44	**56·727**	**30**	**76**
Œsophagus	195	55·666	27	81
	30	**49·700**	**27**	**72**
Stomach	192	52·339	25	79
	118	**52·042**	**20***	**75**
Colon	78	55·372	25	80
	65	**53·276**	**25**	**75**
Rectum	267	54·086	16†	84
	224	**51·437**	**20**	**79**
Anus	5	61·800	51	73
	7	**66·857**	**47**	**81**

* Microscopically a colloid spheroidal cell carcinoma.

† Diagnosis, unconfirmed by autopsy or microscopic examination. Digital examination revealed a large growth in the rectum partially colloid.

The Greater Prevalence of Cancer of the Alimentary Tract in Males.

With regard to the greater prevalence of cancer of the alimentary tract in males it is to be noted that the difference in favour of men is even greater than appears by the total

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numbers occurring in each sex. The fact that 1,656 men suffered from cancer of the alimentary tract against 565 women needs further correction by the facts: 1°, that the number of beds given up to cancer of men in the special wards of the Middlesex Hospital is only one-fourth the number given up to women, and, 2°, that in the general wards of the Hospital, whence an undetermined but considerable number of the cases included in the statistics are drawn, the number of beds for males slightly exceeds that for females. How great an effect these two factors produce it is difficult to say, but since the total number of females included in the complete present investigation (4,659) is more than two and a quarter times as great as the total number of males (2,073), it would appear that the ratio between observed male and female cancer of the alimentary tract (1,656 : 565) should be multiplied by that factor. That is to say, the experience of the Middlesex Hospital would indicate that cancer of the alimentary tract in males is approximately seven (*i.e.* $3 \times 2\frac{1}{4}$) times as great as it is in females.

This greater prevalence of cancer of the alimentary tract in males shows itself in the individual portions of that tract without exception, for the figures in the case of cancer of the anus are so small that the slight difference in favour of women may be only accidental. Nevertheless, the degree of prevalence is not the same throughout. Of cancer of the lip the records contain thirty times as many men as women, but in the case of the tongue (6·13 : 1), other parts of the mouth (6·0 : 1), and œsophagus (6·5 : 1), there is a fair uniformity of six men for one woman. Passing along the alimentary tract the ratio still further diminishes. In the stomach the ratio is 1·6 male to 1 female; in the colon, 1·2 male to 1 female; in the rectum, 1·19 male to 1 female; and at the anus (although this point cannot be pushed too far owing to the small number of cases), 0·7 male to 1 female. Thus the difference in liability of men and of women to suffer from cancer of the alimentary tract gradually and uniformly diminishes as the seat of primary growth is lower in that tract. Whether the slight exception to the uniformity of the diminution that is seen to occur in the case of œsophagal cancer is more than an accident it is impossible to say.

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The Age of Liability to Cancer of the Alimentary Tract.

The mean age for males in the case of cancer affecting all parts of the alimentary tract is 55·076 years; in the case of females it is 52·563 years, showing that cancer in this region affects men, on an average, 2½ years later than women. Leaving on one side cancer of the lip in women, owing to its exceptional rarity, and cancer of the anus in both sexes, owing to the small number of cases, it is noticeable that a great difference obtains on comparing the various parts of the tract. In all regions, except that of the "mouth" (which excludes tongue and lip), the mean male age is later than the female. But whereas there is a difference of as much as six years when the œsophagus is the seat of growth, there is practical identity of age when the stomach is affected. Taking the stomach, colon, and rectum, there is a gradually increasing divergence of the mean ages, the differences between the mean ages for the two sexes being ·29 years, 2·10 years, and 2·6 years.

It is possible in some degree to differentiate between the types of growth concerned in the cancers of the alimentary tract. Probably but little error will be introduced if we regard the cancers of the lip, tongue, other parts of mouth, œsophagus, and anus, as squamous cell carcinomata. With regard to the stomach, colon, and rectum, the matter is more doubtful, and although it is probable that the greater number of these were columnar cell carcinomata, it is inadvisable to separate them into spheroidal cell and columnar cell carcinomata. In any case there are marked differences, both morphological and functional, between the type of epithelium present and squamous cell epithelium.

Grouping the cases after this fashion it appears in cancer of the alimentary tract that the disease occurs, on an average, distinctly later when the primary site is one which is usually attacked by carcinoma of the squamous cell type. Further reference to this point will be made later (p. 43).

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The Liability to Cancer of the Alimentary Tract in Different Quinquennial Age-Periods.

TABLE III.

Table showing percentage occurrence of Cancer of the Alimentary Tract in the various Quinquennial Age-periods.

(The figures for females are printed in heavy type.)

Age	15 to 19.	20 to 24.	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74.	75 to 79.	80 to 84.	85 to 89.
Lip	—	—	0·4	—	4·4	6·6	11·9	14·6	14·6	16·0	9·7	12·3	5·7	3·5	—
	—	—	—	—	—	—	—	**28·6**	**28·6**	—	**28·6**	**14·3**	—	—	—
Tongue	—	0·2	—	—	3·0	10·7	17·7	22·8	15·1	14·4	7·9	6·0	1·1	0·4	0·2
	—	—	**2·8**	**2·8**	**10·0**	**8·6**	**18·5**	**17·4**	**12·8**	**7·1**	**10·0**	**8·6**	**1·4**	—	—
Mouth	—	0·3	0·3	0·3	4·2	9·8	12·8	16·7	19·7	20·8	6·1	6·8	1·1	0·3	0·3
	—	—	—	**4·5**	**6·8**	**6·8**	**6·8**	**13·6**	**18·2**	**13·6**	**13·6**	**9·1**	**6·8**	—	—
Œsophagus	—	—	1·5	1·0	1·0	5·6	12·3	17·4	26·7	22·0	8·2	3·1	0·5	0·5	—
	—	—	**3·3**	**10·0**	**3·3**	**13·3**	**13·3**	**26·7**	**10·0**	**10·0**	**6·7**	**3·3**	—	—	—
Stomach	—	—	2·6	2·0	4·1	9·3	16·6	23·9	18·7	10·9	6·7	4·1	0·5	—	—
	—	**0·8**	**0·8**	**3·2**	**3·5**	**11·8**	**12·7**	**15·3**	**15·3**	**22·0**	**5·1**	**1·7**	**1·7**	—	—
Colon	—	—	1·3	—	3·8	9·0	14·1	23·1	12·8	11·5	17·9	2·6	3·8	—	—
	—	—	**1·5**	**1·5**	**3·1**	**13·5**	**10·8**	**15·4**	**20·0**	**16·9**	**9·2**	**1·5**	**1·5**	—	—
Rectum	0·4	1·5	1·9	3·7	4·5	11·2	9·9	15·7	13·1	16·5	13·5	6·0	1·9	0·4	—
	—	**0·4**	**4·9**	**4·9**	**7·5**	**9·3**	**10·2**	**19·1**	**14·2**	**16·9**	**7·1**	**3·1**	**1·7**	—	—
Anus	—	—	—	—	—	—	—	20·0	—	60·0	—	20·0	—	—	—
	—	—	—	—	—	—	**14·3**	—	—	**28·6**	**14·3**	**14·4**	**14·3**	**14·3**	—

In considering the figures in Table III. along with those in Table II. it is noticeable that the mean age frequently does not fall within the quinquennial age-period of maximum liability. Thus the mean age of the female cases of cancer of the œsophagus is 49·7 years, whereas the maximum incidence falls in the quinquennium 50-54. So too the mean age for cancer of the stomach (female) is 52·042 years, while the greatest number of cases actually occurred during the quinquennium 60-64. The explanation of this divergence is clear. A glance at the tables shows, in practically all instances, that a greater number of cases occurs previous to the quinquennial age-period of maximum liability than occurs subsequently.

Males.—The sites of growth which show the earliest quinquennial age-period of maximum liability are tongue, stomach, and colon (age 50 to 54.) Œsophagus follows with a maximum liability during the quinquennium 55-59; while lip, mouth

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(excluding lip and tongue), rectum and anus, all show a maximum liability to cancer during the age-period 60-64.

Females.—Omitting consideration of the figure for the lip and anus the following points may be noticed. The site of growth which shows the earliest quinquennial age-period of maximum liability is the tongue (age 45-49); next come the œsophagus and the rectum (50-54); next the mouth (excluding lip and tongue) and the colon (55-59); while the latest quinquennial age-period of maximum liability (60-64) is shown by the stomach.

II.—GLANDS ACCESSORY TO THE ALIMENTARY TRACT.

The Liver and Bile Passages and the Pancreas.

With regard to these two glands an important difference must be noted. From the fact that a liver which is the seat of new growth can frequently be recognised as enlarged and bossy during life, whereas cancer of the pancreas as such cannot be diagnosed during life, it appears, 1°, that the total number of cases of cancer of the liver in our records exceeds the number of cases of cancer of the pancreas; 2°, that cancer of the pancreas has almost invariably been diagnosed in the records of the Hospital as the result of post-mortem examination; and 3°, that in the cases of malignant disease of the liver, not verified by post-mortem, although there is no reason to doubt that this organ was the seat of cancer, it is impossible to determine whether the growth there was primary or secondary. From the standpoint of our present knowledge we should incline to believe that the great majority of them were metastases from some unrecognised primary growth. Figures obtained in the case of the pancreas, therefore, have a relatively high probability of accuracy. Those for the liver a relatively low one. In some measure the difficulty of dealing with the figures for the liver has been overcome by Dr. Colwell, who, in the course of his investigations on this organ,* has carefully examined the post-mortem histories of

* This volume p. 122.

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the patients in this class who died, and has divided them into those which may reasonably be regarded as primary and those which are probably secondary. Hence for the liver two sets of figures are given below; the one in which all hepatic cases are dealt with together as has been done for the rest of the statistics in this paper, the other dealing alone with such cases as were shown by their post-mortem records to be almost certainly primary cancer of the liver or bile passages.

The mean age for males (61 cases) of the entire liver series of cases is 53·836 years, for females (70 cases) it is 55·414 years. Dealing with the selected liver series the figures are—males, 52·9 years; females, 54·1 years.

In the case of the pancreas the mean age of the males (15 cases) is 57·2 years, for females (17 cases) 54·414 years.

TABLE IV.

Percentage occurrence of Cancer of the Liver and of the Pancreas in the various Quinquennial Age-periods.

(The figures for females are printed in heavy type.)

Age	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74
Liver and bile passages unselected.	11·5	9·8	14·8	9·8	18·0	26·2	6·6	3·3
	5·7	**17·1**	**11·4**	**7·1**	**11·4**	**27·1**	**12·9**	**7·1**
Liver and bile passages selected.	7·5	15·0	12·5	12·5	17·5	27·5	7·5	—
	3·3	**10·0**	**13·3**	**16·6**	**20·0**	**23·3**	**10·0**	**3·3**
Pancreas	6·6	6·6	—	20·0	20·0	20·0	20·0	6·6
	—	**11·9**	**17·6**	**23·6**	**11·9**	**17·6**	**17·6**	—

III.—THE GENERATIVE SYSTEM.

Under this heading are included in the male, the penis, scrotum and prostate; in the female, the uterus, vagina and vulva. It has not been thought advisable to take into consideration either the testicle or ovary. For primary growths of the testicle are frequently complex, and rarely of a nature that can be definitely regarded as carcinomatous even from the microscopic point of view; while growths

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of the ovary, although often bearing resemblances to carcinoma of the columnar cell type, are usually separated from this group.

TABLE V.

Table showing the Mean Minimum and Maximum Ages observed at the Middlesex Hospital in cases of Cancer of the Generative System.

MALES.					FEMALES.				
Site of Primary Growth.	No. of Cases.	Mean Age in Years.	Minimum Age in Years.	Maximum Age in Years.	Site of Primary Growth.	No. of Cases.	Mean Age in Years.	Minimum Age in Years.	Maximum Age in Years.
Penis - -	62	52·290	22	79	Uterus -	1,971	46·707	22	79
Scrotum -	36	47·417	31	70	Vagina -	40	49·725	23	74
Prostate -	10	67·400	55	73	Vulva -	88	55·682	27	87

In the case of the generative system the most striking point is the vast preponderance of female cases. This preponderance concerns the uterus itself, since the figures for vagina and vulva do not differ greatly from those for penis and scrotum. If we regard the prostate as the male homologue of the uterus the difference becomes even more striking. The percentage of cancer of the female generative tract to the total female cancer is 45 per cent. The mean age of liability of males to cancer of the generative tract is distinctly later than the age of liability of females. The age of liability to cancer of the scrotum—which is the earliest mean age for males of all the series examined in this paper—probably bears a close relation to the generally accepted view that the large majority of patients suffering from this form of the disease are chimney sweepers. Despite the small number of cases it is noteworthy that cancer of the prostate has the latest mean age of any of our series.

The generative system also supplies the earliest mean age for females, viz., 46·7 years in the case of cancer of the uterus. The mean age becomes later as one passes outwards, the mean age of liability to cancer of the vagina being three

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years later than that for the uterus, and the mean age for cancer of the vulva being six years later than that for the vagina. A corresponding difference obtains in reference to the earliest ages at which the various sites of the female generative tract are the seats of cancer.

TABLE VI.

Table showing percentage occurrence of Cancer of the Generative Tract in the various Quinquennial Age-Periods.

Age	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69	70 to 74	75 to 79	80 to 84	85 to 89
Penis	3·2	1·6	4·8	9·6	11·2	12·9	14·5	6·4	12·9	11·2	8·1	3·2	—	—
Scrotum ...	—	—	8·3	8·3	25·0	13·8	25·0	13·8	2·7	—	2·7	—	—	—
Prostate ...	—	—	—	—	—	—	—	10·0	20·0	20·0	50·0	—	—	—
Uterus	0·4	3·7	7·4	14·1	18·2	18·3	15·7	9·6	7·3	3·3	1·1	0·6	—	—
Vagina	2·5	—	5·0	7·5	20·0	20·0	15·0	2·5	15·0	10·0	2·5	—	—	—
Vulva	—	1·3	3·4	4·5	6·8	11·4	15·9	19·3	17·0	6·8	8·0	3·4	—	2·3

From the foregoing table it is seen that the maximum liability to cancer of the penis is in the age-period 50–54, and for cancer of the prostate 70–74. In the case of the scrotum there are two maxima during the age-periods 40–44 and 50–54.

The maximum liability to cancer of the uterus and of the vagina occurs during the ten-year age-period 40–49. The maximum liability in the case of the vulva lies in the quinquennium 55–59.

IV.—OTHER SITES OF PRIMARY CANCER.

(i) The Breast.

For the breast the main age of liability to cancer amongst women is 51·434 years, with an earliest observed case of 22 years and a latest observed case of 89 years. Amongst men, cancer of the breast has occurred in 20 cases, and the

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mean age of these was 53·95 years, with a minimum of 40 years and a maximum of 86. The percentage occurrence in the quinquennial age-periods is as follows:—

Age	20 to 24.	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74.	75 to 79.	80 to 84.	85 to 89.
Males ...	—	—	—	—	30·0	10·0	20·0	15·0	10·0	5·0	5·0	—	—	5·0
Females ...	0·1	1·0	4·0	8·2	14·8	16·9	16·3	14·2	12·3	6·8	3·4	1·4	0·2	0·2

From these figures it appears that nearly two-thirds of all breast cases in women occur between the ages of 40 and 60, and are fairly evenly distributed throughout the four quinquennia composing this period. Nevertheless, the actual maximum occurs in the quinquennium 45–49. Cancer of the breast constitutes 37·8 of all female cancer.

(ii) The Urinary Bladder.

Though there is no doubt that primary cancer of the urinary bladder occurs, considerable difficulty arises when considering the question, from two points of view. Firstly, cancer of the bladder occurs under two forms at least, one of which is a squamous cell carcinoma similar to that met with ordinarily and in other situations, *e.g.* lip and tongue; and the other of which is composed of "transitional" cells, which in its appearance and arrangement presents considerable differences from the usual type of squamous cell carcinoma. Secondly, in the female there is frequently a difficulty in deciding whether the bladder has been invaded by a cancer starting at the cervix or the vulva, or whether these parts have been invaded by a growth originating in the bladder itself. In the male, on the contrary, the probability is largely in favour of the view that a cancer of the bladder is primary.

The mean ages of liability to cancer of the bladder as determined from the cases that have occurred at the Middlesex Hospital are relatively late, and show but little difference in the two sexes, being 59·920 years for 25 male cases and 59·478

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for 23 female cases. The percentage occurrence in the various quinquennial age-periods are as below :—

	Age	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74.	75 to 79.
Males		—	12	28	8	8	28	12	4
Females		8·7	4·3	8·7	30·4	21·7	13·0	8·7	4·3

(iii) The Skin.

Under this heading are included such cases of cancer of the cutaneous surfaces as were not situated on the face, which is usually affected by rodent cancer. Hence the situations in which the growths were found vary considerably, but usually were the scalp or the lower part of the limbs, particularly the hand and forearm. As will be seen, cases of rodent cancer are dealt with separately in the succeeding section. The mean age of liability to cancer of the skin amongst men (43 cases) is 60·333 years; amongst women (37 cases) is 55·946 years. The liability in the various quinquennial age-periods is as follows :—

	Age	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74.	75 to 79.	80 to 84.
Males		—	4·6	6·9	6·9	9·3	6·9	27·9	16·2	6·9	9·3	4·6
Females		5·4	—	13·5	16·1	8·1	5·4	21·6	16·2	8·1	5·4	—

(iv) Rodent Cancer.

In a large proportion of the clinical histories a diagnosis of "rodent ulcer" was definitely given to cases in this class, but when the part affected was the face, in the region of the eyes or nose, a clinical diagnosis of "cancer of the face" was replaced for our present purpose by one of "rodent cancer." It is probable, however, that a certain amount of error has been introduced unavoidably by the inclusion of

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some cases of squamous cell carcinoma beginning in the lip or cheek. In the absence of histological examination it is impossible to avoid such error completely, although special attention has been paid to the absence of secondary growth in lymphatic glands.

The mean age of liability to rodent cancer appears to be for males (119 cases) 58·261 years, for females (83 cases) 59·374 years. From our present knowledge the ages of 28 years (male) and 31 years (female) as the ages of the earliest observed cases, seem abnormally young, and possibly these were in reality cases of squamous cell carcinoma.

The percentage liability to rodent cancer in the various quinquennial age-periods is as follows :—

Age	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74.	75 to 79.	80 to 84.	85 to 89.
Males ...	0·8	3·3	1·7	5·9	10·9	14·3	12·6	18·5	13·5	10·9	5·9	0·8	0·8
Females ...	—	1·2	4·8	2·4	16·8	13·2	7·2	10·8	21·6	13·2	7·2	1·2	—

(v) The Larynx.

It has already been remarked that difficulty arises in the case of cancer of the larynx, owing to the liability of the œsophagus to disease in the immediate neighbourhood of the larynx. Subject to this source of error the mean age for cancer of the larynx in males (26 cases) is 55·954 years, for females (5 cases) it is 53·6 years. The quinquennial age-liability is as follows :—

Age ...	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74.
Males ...	3·8	—	23·1	23·1	15·4	19·2	7·7	7·7
Females ...	—	—	20·0	60·0	—	20·0	—	—

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V.—COMPARISON OF FIGURES IN PRECEDING SECTIONS.

In order to arrive at a conclusion concerning the relatively early or late occurrence of any particular form of cancer, whether considered histologically or with reference to its site, it is necessary to bear in mind that neither the mean age of liability nor the quinquennial age-period of maximum incidence is alone sufficient. Each of these factors gives a certain amount of information, but each is incomplete in itself. Hence, it is desirable to obtain some expression of both sets of figures. The simplest way in which this can be done is to use for purposes of comparison the product of the ascertained mean age and the middle year of the quinquennial age-period of maximal liability. For example, in the case of figures for the male lip, the mean age is 58·668 years, but the maximum number of cases occurs during the quinquennial age-period, 60–64. The actual liability to cancer of the lip is better represented for purposes of comparison by the quantity $55{\cdot}668 \times 62$ than by either the mean age or the quinquennial age-period of maximum liability alone.

Further, for purposes of comparison it is necessary to have a figure representative of the whole series of cancer cases, male and female. This figure has been obtained in the same way as the others, and is an expression of the product of the mean age and the quinquennial age-period of greatest liability. Since from the entire set of figures at our disposal the mean age of liability to all forms of cancer for males is 55·205 years, and for females is 49·929 years, and since by a separate estimation the quinquennial age-period of maximum liability to cancer has been found to be 50–54 in the case of males, and 45–49 in the cases of females, $55{\cdot}205 \times 52$, *i.e.* 2870·66, must be taken as the standard against which the male figures for cancer are to be measured, and $49{\cdot}929 \times 47$, *i.e.* 2346·663, the corresponding standard for the female figures. Omitting, for convenience, the decimal figures and taking the square roots of the sums, we obtain 53·6 years as the standard age for cancer in males and 48·4 years for females. Taking then the figures that have been given in the preceding sections and treating them in this manner, it will be possible to arrange the situations of primary cancerous growth according

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to the ages at which they are liable to occur. This has been done in Table VII.

TABLE VII.

Table showing the various Sites of Primary Cancer arranged in order of the computed ages at which they are liable to occur.

(Compiled from 2,073 male and 4,659 female cases in the Records of the Middlesex Hospital.)

	MALES.				FEMALES.			
Age.	Site of Growth.	I.	II.	III.	Site of Growth.	I.	II.	III.
45 to 49	Breast ...	52·263	42	**46·8**	Uterus ...	46·707	47	**46·8**
	Scrotum ...	47·417	47	**47·2**	Vagina ...	49·725	45	**47·3**
					Breast ...	51·434	47	49·2
					Tongue ...	52·171	47	49·5
50 to 54	Penis ...	52·290	52	**52·1**	Œsophagus	49·700	52	50·8
	Stomach ...	52·339	52	**52·2**	Rectum ...	51·437	52	51·7
	Larynx ...	55·954	50	**52·9**	Larynx ...	53·600	52	52·8
	Tongue ...	54·587	52	**53·4**	Pancreas ...	54·414	52	53·2
	Colon ...	55·372	52	53·7				
55 to 59	Bladder A	59·920	52	55·8	Colon ...	53·276	57	55·1
	Œsophagus	55·666	57	56·3	Vulva ...	55·682	57	56·3
	Liver ...	53·836	62	57·8	Stomach ...	52·042	62	56·8
	Rectum ...	54·086	62	57·9	Mouth (excluding lip and tongue)	56·727	57	56·9
	Mouth (excluding lip and tongue)	55·314	62	58·5	Bladder ...	59·478	57	58·2
					Liver ...	55·414	62	58·6
	Pancreas ...	57·200	60	58·6	Skin ...	55·946	62	58·9
					Lip ...	60·714	52	59·7
Above 60	Rodent cancer.	58·261	62	60·1				
	Lip ...	58·668	62	60·3	Rodent cancer.	55·374	67	63·1
	Skin ...	60·233	62	61·1				
	Anus ...	61·800	62	61·9	Anus ...	66·857	62	64·4
	Bladder B	59·920	67	63·4				
	Prostate ...	67·400	72	69·7				

Note.

Column I. gives the mean age of all cases for each site.

Column II. gives the mean age of the quinquennial age-period in which the maximum number of cases occurred.

Column III. gives the ages of liability computed by taking the square roots of the product of the corresponding quantities in Columns I. and II. Figures in heavy type are those *below* the mean computed age for all cancer in the same sex.

Two values are given for the male bladders, since two quinquennial age-periods of maximum occurrence of cases appear in the series, and are too widely divergent to be represented by one intermediate number.

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From the foregoing table it appears that the range of years over which cancer is liable to occur is practically the same, viz. 46–64 in both sexes; for the extreme lateness of cancer of the prostate, according to our figures, is not of sufficient reliability, owing to the small number of cases.

It must be remembered, however, that cancer of the uterus and of the breast constitute over 80 per cent. of our entire series; so that, excluding these, the actual number of cases represented on the female side of the table is only about half that represented on the male side.

This same preponderance of uterine and mammary cancer, combined with the relatively low mean ages at which they occur, explains how the larger number of "sites of growth" in women occur at ages later than the mean computed age, while in males the distribution is far more regular. Thus in males cancer of the breast and scrotum tends to occur *early;* cancer of the penis, stomach, larynx, tongue, and colon tends to occur at *about the average age;* cancer of the œsophagus, liver, rectum, mouth, and pancreas tends to occur *late;* and rodent cancer, cancer of the lip, skin, anus, bladder, and prostate tends to occur *very late.* In the case of females such a rough division of "sites of growth" is more difficult to make. Nevertheless, the uterus and vagina are situations in which cancer tends to occur *early;* the breast and tongue are liable to be affected at *about the average age* or a little later; the œsophagus, rectum, larynx, pancreas, colon, vulva, stomach, and mouth tend to be affected with cancer *late;* while cancer of the bladder, liver, skin, lip, anus, and rodent cancer tend to occur *very late.*

Broadly speaking, then, it may be said that in both sexes the generative system, including therewith the breast, affords the early cases of cancer, that the cutaneous system affords the late cases of cancer, and that the intermediate group is afforded by the alimentary system.

With regard to a division of sites of cancer according to the histological characters of the growth usually met with at those sites, it is clear that a consideration of Table VII. gives no help. It is true that since the cutaneous system affords the late cases, squamous cell carcinoma also occurs late; but a glance at the table shows that squamous

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cell carcinoma is to be found distributed through the "early," "average," and "late" classes indiscriminately. The most that can be said for spheroidal and columnar cell carcinomata is that they occur about the middle of the list; but since this intermediate group contains the alimentary tract, and since a considerable portion of the spheroidal cell carcinomata are constituted by the breast, which has been included in the "early" group, it is clear that no argument can be based thereupon. Consequently, it is impossible to say that any particular variety of epithelium, whether squamous, columnar, or spheroidal, tends to become the subject of carcinomatous change either earlier or later than any other variety. The table affords no evidence that the early or the late appearance of a carcinoma at any given site depends upon the character of its epithelium.

It is true that in the alimentary tract those situations which are clothed with squamous epithelium are usually affected by cancer later than those clothed by the other varieties of epithelium (p. 33), and there is a certain small value in such a comparison between parts of the same tract. But even here the indications are not sufficiently clear to warrant our belief that the character of the epithelium exerts a determining influence. Although we are accustomed to hold that squamous epithelium is "more resistant" than either columnar or spheroidal epithelium, this greater resistance does not prevent the cervix, vagina, scrotum, penis, and tongue from forming some of the situations in which the tendency for the occurrence of cancer is earliest.

VI.—CANCER BEFORE THE AGE OF 35 YEARS.

In dealing with this branch of the subject, difficulty arises owing to the greater probability of error introduced by the accidental inclusion of cases of sarcoma. All that can be said is that special attention has been paid to this point while collecting the statistics, and that it is believed that the error is a relatively small one.

Of the 2,073 male cases, 54, or 2·60 per cent., occurred in persons under the age of 35 years; of the 4,659 female cases, 366, or 7·86 per cent., were under the age of 35 years.

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The distribution of the cases in the two sexes can be seen by a reference to Table I. From this table it appears that in males cancer of the alimentary tract accounted for 40 cases, or 2·4 per cent. of the entire series of male cancer of the alimentary tract, and that in 9 cases, or 8 5 per cent. of the entire generative series, cancer affected the generative tract. The latter figures are a further indication of the relatively early age at which cancer of the generative tract occurs in males. In females, cancer before the age of 35 is almost entirely made up of cancer of the uterus (227 cases) and of the breast (90 cases). The cancer of the female generative system before the age of 35 years constitutes 11 per cent. of the entire cancer of the female generative system; cancer of the breast before the age of 35 constitutes 5·1 per cent. of the entire cancer of the breast; cancer of the alimentary tract constitutes 7·4 of the entire series for the female alimentary tract. It is clear, therefore, that cancer below the age of 35 years is not only actually more common in females than in males, but also that it constitutes a relatively larger proportion of both the generative and the alimentary series. This corroborates the conclusion expressed elsewhere that cancer affects women earlier than it affects men. It is unnecessary to state that the actual figures in both sexes increase with the quinquennial age-periods, being greatest in the age-period 30–34.

SUMMARY.

As a result of examining 2,073 male and 4,659 female cases of cancer of which records are preserved at The Middlesex Hospital, the following principal conclusions have been drawn:—

(1.) There is a general tendency for males to be affected by cancer at a later age than females, the mean age of all cancer being in males 55·2 years, and in females 49·9 years.

(2.) Cancer of the alimentary tract is about seven times as common in males as in females.

(3.) The difference in liability of men and of women to cancer of the alimentary tract gradually and uniformly

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diminishes as the seat of primary growth is lower in that tract.

(4.) The mean age of liability of males to cancer of the alimentary tract is 55 years, that of females is 52·5 years. Cancer of the liver and bile passages is, however, abnormal, for the mean age of female cases (54·1 years) is higher than that of males (52·9 years). This abnormality depends entirely upon the later age at which women suffer from cancer of the gall-bladder and bile passages (Cf. Dr. Colwell's paper in this volume).

(5.) In males 80 per cent. of all cancer affects the alimentary tract. In females 80 per cent of all cancer affects the generative tract, including therewith the breast.

(6.) In both sexes the generative system, whether including or excluding the breast, tends to be the earliest system affected by cancer. In both sexes the system with the latest tendency to be affected by cancer is the cutaneous. In both sexes an intermediate position is held by the alimentary system.

(7.) No support is afforded by the statistics to the view that the early or late appearance of carcinoma at any given site is determined by the character of its epithelium.

(8.) Cancer before the age of 35 years is commoner in women than in men, and in both sexes shows a special tendency to affect the generative tract.

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STATISTICS OF THE SITE-INCIDENCE OF CARCINOMA BASED ON THE RECORDS OF THE MIDDLESEX HOSPITAL.

By W. S. LAZARUS-BARLOW, M.D., F.R.C.P.,
AND
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It was shown in a recent paper * that the statistics of The Middlesex Hospital yield evidence, after making the necessary corrections, 1° that in the case of women a steady increase in cancer mortality took place amongst populations age 35 † in the various years up to about 1870, but that since that time the mortality has remained stationary; 2° that in the case of men a steady increase in cancer mortality has been taking place from the first and is still progressing.

With the object of ascertaining whether the above increase observed in the cancer mortality at The Middlesex Hospital is affecting every organ or only some, the present research has been undertaken, the idea being entertained that if the increase in cancer were proved to be intimately associated with one particular system or organ, a clue might be given as to the direction in which our investigations should be prosecuted towards establishing the nature and the cure of the disease.

* Arch. Middlesex Hosp., vol. iii., p. 148.

† For the sake of convenience the expression "population derived from The Middlesex Hospital Records, age 35, and healthy," will be represented by the Greek letter Ψ. Thus, Ψ 1850 means the population which was derived from the records of The Middlesex Hospital, and which was age 35 and healthy in the year 1850. The method is somewhat clumsy, but it serves to emphasize the fact that we are referring to cancer deaths in a given "population" and not in a given year.

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I.—METHOD OF OBTAINING STATISTICS.

The figures on which this paper is based are in part those which served for our earlier paper, and in part those specially collected for determining "cancer ages" as given in the paper by one of us on page 26 in the present volume of the Archives. It will be remembered that the cases from our records were considered on the lines of populations at age 35, and cancer cases were balanced against non-cancer cases in the various years. The cancer cases in our age-35 populations have now been sub-divided according to the organ which was the primary site of growth; and, as before, males and females are considered separately. We therefore become possessed of a series of cases of uterine, mammary, rectal, lingual, etc. cancer among our age-35 populations of the different years from 1814 to 1900. These cases, however, are not considered annually, but are arranged in quinquennial groups in order to obtain larger numbers for comparison.

After 1864, however, certain corrections have to be made, for, as explained in our former paper,* in every year from that date onwards there is a lacuna in its age-35 population: this lacuna becomes greater the nearer one approaches to the age-35 population of 1900. The corrections take the form

* *Loc. cit.* In order to determine in some degree the relative value that should be attached to these estimated figures we have applied the principles upon which they were calculated to series of years in which we actually possess the records. Thus, we have assumed that we did not possess the Records for 1884–1903, in two instances, and in a third that we did not possess the Records for 1894–1903. We then calculated out the estimated figures and compared these with *ascertained* figures derived from actual search through the Records 1884–1903. Our results are as follows:—(1) We *estimated* that during the decade 1884–1893, 14 male and 28 female cases of cancer between the ages 66 and 75 would be admitted to The Middlesex Hospital; we *actually found* that 26 male and 39 female were admitted: (2) we *estimated* that 80 male and 190 female cases of cancer between the ages of 56 and 75 would be admitted during the 20 years 1884–1903; the *actual* numbers were 225 male and 265 female: (3) we *estimated* that 27 male and 51 female cases of cancer between the ages of 66 and 75 would be admitted during the decade 1894–1903; the *actual* numbers were 62 male and 80 female. Consequently the lacunary numbers were in all instances under-estimated, and were more under-estimated in the case of males than in the case of females. But considering that the estimated figures for non-cancerous cases are probably also under-estimated in the same way, it is felt that the general conclusions drawn in this and the preceding paper are substantially correct.

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of "estimated figures," which have to be added to the actually "ascertained" figures for the corresponding year.

As in the case of the actually "ascertained" figures, the totals lacking have also been grouped quinquennially, and further have been sub-divided under the headings "Lingual," "Labial," "Mammary," "Uterine," and so on. The basis of sub-division was the number of cases of each sort which are actually recorded at The Middlesex Hospital in each quinquennial age-period; these are set forth in Table I. in the paper on "Cancer Ages" by one of us in the present volume of the archives.*

To take an example, in our population for 1865 we lack persons aged 74; in that for 1866 persons aged 74 and 73; in that for 1867 persons of 74, 73, and 72 years; in that for 1868, those of 74, 73, 72, and 71 years; and in that for 1869 all those between 70 and 74 years of age. These lacking numbers are set forth in the last volume of the Cancer Reports,† where it is found that the "estimated" figures to be added to the "ascertained" cancer figures in males are respectively: For 1865, 2 cases; for 1866, 3; for 1867, 5; for 1868, 6; for 1869, 7; that is to say, for the quinquennium 1865–69, 23 cases have to be added to the "ascertained" male cancer figures in order to include those persons who will die at ages 70–74.

It will be found in Table I. in "Cancer Ages" that in the quinquennial age-period 70–74 there were 141 cases of male cancer, of whom 28 were labial, 26 lingual, 6 œsophageal, 8 gastric, and so on. Hence, if 23 be the "estimated" total to be added to the "ascertained" cancer figures in males for the quinquennium 1865–69, then of these the "labial" factor will be $\frac{28}{141}$ of 23, *i.e.* 4·5, the "lingual" factor will be $\frac{26}{141}$ of 23, *i.e.* 4·2; the "gastric" factor $\frac{8}{141}$ of 23, *i.e.* 1·3; and so on. These are added to the ascertained figures, as set forth in Tables I. and II. of the present paper, dealing with males and females respectively.

We therefore become possessed of the following information:—

Of the persons who were 35 years of age and healthy in quinquennium A, p died of cancer of the lip, while q

* Arch. Middlesex Hosp., vol. v., p. 29.

† Arch. Middlesex Hosp., vol. iii., p. 144.

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died of cancer of the tongue, r of cancer of the œsophagus, and so on.

Of the persons who were 35 years of age and healthy in quinquennium B, p' died of cancer of the lip, while q' died of cancer of the tongue, and r' of cancer of the œsophagus, and so on.

The above facts have been dealt with in two ways: firstly, in reference to the total cancer mortality in the age-35 "population" for the particular quinquennium under consideration; and secondly, in relation to the general mortality, *i.e.*, cancerous and non-cancerous, of that "population." The results are expressed in percentages, and the quinquennial variations in the percentage-incidence of cancer on the different systems and organs both in relation to total cancer-mortality and to total general mortality, have been reviewed, and a comparison has been instituted.

The total number of cancer cases considered in this paper is not identical with that which formed the basis of our paper in the last Report. For in certain instances, though the diagnosis of "cancer" was reliable, the actual primary site was not given. Hence such cases were valueless for our present purpose. On the other hand, cancer cases occurring during 1904 which were not included in our previous paper have been utilised for the present one. Actually, the number of observed cancer cases upon which this investigation has been based is 6,290, viz., 2,019 males and 4,271 females. These are given in detail in Tables I. and II. at the end of the paper.

I.—CANCER AT DIFFERENT PRIMARY SITES AMONGST AGE-35 POPULATIONS CONSIDERED IN REFERENCE TO THE CANCER MORTALITY.

The Alimentary Tract.

LIP.—*Males.*—A comparison of the figures in the various quinquennia throughout the century as set forth in Table III. shows that up to about Ψ * 1879 a marked decrease took place in the percentage-incidence of labial cancer. A great fall took

* See note, p. 47.

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place about Ψ 1840, before which date the percentage was throughout above 20 %, and in the earlier quinquennia attained a much higher figure. From Ψ 1840 to Ψ 1879 the decline was much more gradual, but the percentage-incidence in the quinquennial period Ψ 1875–79 is barely half that of the quinquennium Ψ 1840–44. In Ψ 1879 the low-water mark appears to have been reached, and during the last two Ψ decades of the century the percentage occurrence of cancer of the lip evinces a tendency to rise, so that instead of being 7·22, the percentage recorded for Ψ 1875–79, it theoretically attained the height of 9·76 in the quinquennium Ψ 1895–99.

Females.—Owing to the paucity of the cases, statistics concerning lip cancer in women cannot have such a high relative value as in males; nevertheless, if the evidence afforded by the figures in Table IV. be of any account, it would seem to indicate that a slight decrease in cancer of the lip has taken place in women.

TONGUE.—*Males.*—During the second half of the nineteenth century (Ψ), the percentage occurrence of lingual cancer has altered but slightly. Prior to Ψ 1855, however, the percentage incidence was distinctly lower, and in only the quinquennium Ψ 1835–39 was 20 per cent. attained, whereas after Ψ 1855 the percentage has been invariably higher than 20. The highest recorded figure was in the quinquennial period Ψ 1870–74; in the three succeeding quinquennia the percentage fell slightly, but during the last Ψ decade of the century there has been a theoretical rise. Nevertheless, considering the large proportion of the "corrected figures" formed by the "estimated figures," too great reliance must not be placed upon the evidence yielded by these last 10 years.

Females.—Cancer of the tongue in women shows, on the whole, a distinct tendency to diminish, and during the last 40 (Ψ) years of the century the percentage-occurrence has been always below 2, whereas in the quinquennia preceding 1860 (Ψ) the percentage was almost uniformly above that number.

OTHER PARTS OF THE MOUTH, INCLUDING THE CHEEK.—*Males.*—The percentage-incidence of cancer in this region has, on the whole, distinctly increased. From Ψ 1825 to 1864, there was an almost steady rise from 6·89 to 16·29, which is

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the highest recorded figure. During the next Ψ decade a slight fall occurred, succeeded however by another rise in the quinquennium Ψ 1875–79, during which period a percentage was attained almost equalling that of Ψ 1860–64. During the last 20 years of the century (Ψ) there has been a lower percentage, and the occurrence of the disease in this situation has not been so great as it was in the 20 years preceding Ψ 1875, although considerably higher than in the quinquennia of the first half of the century. Moreover, if any reliance at all can be placed upon the numbers for the last quinquennium (Ψ) it would appear that there is at present a slight tendency to increase.

Females.—The percentage-incidence of cancer at this site is a small one throughout the century, and although variations of an irregular character were exhibited in the years (Ψ) preceding 1875, yet in the last quarter of the century (Ψ) a diminution in the percentage-occurrence can be discerned.

ŒSOPHAGUS.—*Males.*—Our statistics relating to œsophageal carcinoma in males show that a more or less gradual increase in the percentage-occurrence of primary cancer of this portion of the alimentary tract obtained throughout a period of sixty years (Ψ) extending from Ψ 1825 to Ψ 1884, at which latter date the maximum incidence of 14·11 per cent. was attained. The even nature of the course of increase is broken by two irregularities, one of which occurred in the quinquennium Ψ 1830–34, when the percentage rose from 3·44 to 10·52, and then as rapidly fell to 3·07; the other break in the course took place in the quinquennial period Ψ 1860–64, when the percentage suddenly increased from 6·21 to 10·13, and then fell immediately to 6·06.

During the last three quinquennia (Ψ) of the century the percentages, although lower than those attained in the decade Ψ 1875 to Ψ 1884, nevertheless exceed those which characterize the earlier years of the century; the large part played by the "estimated figures," however, must be borne in mind.

Females.—Cancer of the œsophagus apparently increased in frequency in females between Ψ 1850 and Ψ 1879; the period of maximum incidences being the quinquennium Ψ 1875–79, that is to say, the period of maximum occurrence was attained five years before it was reached in the case of

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men. A distinct decline is noticeable during the closing years of the century.

STOMACH.—*Males.*—Up to Ψ 1845 there were considerable irregularities in the percentage incidence of gastric cancer in men, but during the next 30 years (Ψ) a steady increase took place, and in the quinquennium Ψ 1870–74 the percentage reached the figure 10·80. During the last quarter of a century (Ψ) the percentage has varied in the different quinquennia to the extent of rather over 2 per cent., but the percentages recorded during this period are distinctly higher than those of the 25 years (Ψ) preceding 1870. The statistics of The Middlesex Hospital seem therefore to indicate that carcinoma of the stomach in males exhibits a tendency to increase.

Females.—Cancer of the stomach in women apparently underwent a gradual increase between Ψ 1830 and Ψ 1849; during the three succeeding quinquennia (Ψ) there was a decreased frequency, followed again by a rise up to Ψ 1879, when the maximum was attained. During the last 20 years (Ψ) gastric carcinoma in women appears to have remained fairly constant, with perhaps a very slight tendency to decline in frequency.

COLON.—*Males.*—There has been a distinct though rather irregular course of increase of carcinoma of the colon in men, extending over a period of almost 60 years (Ψ), the maximum being attained in the quinquennium + 1880–84. A higher figure, however, was recorded for the quinquennial period Ψ 1825–29, but owing to the paucity of the total number of cancer cases in our age-35 populations for that period, too much reliance must not be placed upon the accuracy of that percentage. During the last 15 years of the century (Ψ) there has on the whole been a slight tendency to a decline.

Females.—As in the case of œsophageal cancer in women the maximum percentage occurrence of carcinoma of the colon was attained in Ψ 1875–79. During the quinquennia preceding Ψ 1875 there was a distinct if somewhat irregular increase, and since Ψ 1880 there seems to have been a slight tendency to a decline in the frequency of carcinoma of this portion of the large intestine.

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RECTUM AND ANUS.—*Males.*—In the case of men there was a general tendency to an increased frequency of rectal and anal cancer up to Ψ 1869; the maximum percentage-occurrence being attained in the quinquennial period Ψ 1865–69. During the last thirty years (Ψ) the percentage-incidence, though lower than that of the quinquennium just mentioned, has remained at an approximately constant high level. On the whole, therefore, it would appear that rectal and anal cancer in men has undergone an increase during the century.

Females.—Cancer of the rectum and anus in women did not reach its maximum till the quinquennium Ψ 1885–89, that is to say, 20 years (Ψ) later than the corresponding high-water mark in male cancer of this portion of the gut. Up till Ψ 1889 there was a distinct gradual increase in the percentage occurrence, but during the last decade (Ψ) of the century there has been a slightly diminished incidence, which on account of the larger part played by the estimated figures, should not be taken too seriously. The increased percentage occurrence of anal and rectal cancer is largely responsible for the increase in cancer of the alimentary tract as a whole in the female sex.

Summary of Cancer of the Alimentary Tract.

A consideration of Table V. reveals the fact that a distinct increase in the percentage incidence of cancer of the alimentary tract has been taking place throughout the century in the case of both males and females. In the case of male cancer of the alimentary tract, the several portions of this system individually share in the increase, for although cancer of the lip at first most certainly diminished, yet there is evidence that this form of cancer has been increasing in the age-35 populations of the last 20 years.

As regards women, the increase is not so uniformly distributed throughout the whole alimentary tract: thus labial, lingual, and buccal cancer show a distinct tendency to diminish; cancer of the œsophagus reached its maximum in the age-35 population of the quinquennium 1875–79, but in those since 1880 has declined in frequency. Cancer of the rectum and anus appears to be largely responsible for the increase in female cancer of the alimentary tract as a whole.

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The relation between cancer of the alimentary tract in females and uterine and mammary cancer is shown graphically on p. 62. From these curves it appears that though the incidence of cancer in these three regions has run, speaking generally, on parallel lines, yet the alimentary tract attains a higher level than either breast or uterus.

Glands Accessory to the Alimentary Tract.—The Liver and Bile Passages, and the Pancreas.

LIVER AND BILE-DUCTS.—*Males.*—From Ψ 1830 to Ψ 1859 there was a distinct increase in primary cancer of the liver and bile-ducts. This was followed by a sudden fall in Ψ 1860–64; in the next quinquennium (Ψ) the percentage again rose, and has continued at a fairly constant level throughout the rest of the century. The figures recorded for these last Ψ 35 years, however, are distinctly lower than those which characterize the earlier half of the century, but it is quite possible that the number of secondary hepatic disease inadvertently included was greater in the first half of the century.

Females.—The variations in the percentage-occurrence of primary cancer of the gland and its ducts in females exhibit a high degree of irregularity; nevertheless it appears that primary carcinoma of this portion of the body has been less common during age-35 populations of the last 20 years than in those of the two preceding decades.

PANCREAS.—*Males.*—Many of the quinquennia up to Ψ 1865 are entirely deficient in cases of pancreatic cancer in men, and it must also be borne in mind that the "estimated" figures form a steadily increasing proportion of the "corrected figures" in the Ψ quinquennia which succeed the date above mentioned. On the whole, therefore, it must be admitted that no very reliable information is forthcoming regarding the percentage-incidence of carcinoma of the pancreas.

Females.—The above remarks as to carcinoma of the pancreas in males are equally applicable to pancreatic cancer in women, for only 5 cases are recorded in the quinquennia up to Ψ 1865.

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Generative Tract.

PENIS.—*Males.*—A review of the percentages recorded in the different quinquennia (Ψ) throughout the century seems to indicate that carcinoma of the penis has remained approximately constant. If one exclude the decade Ψ 1820–30, then the maximum frequency was attained in the quinquennial period Ψ 1850–54.

SCROTUM.—As in the case of carcinoma of the penis, carcinoma scroti has remained fairly constant since Ψ 1835. The maximum was attained in the quinquennial period Ψ 1860–64.

PROSTATE.—The number of cases of prostatic carcinoma is so limited that very much reliance cannot be placed upon the evidence which they yield as to the incidence of the disease on this part of the male generative system; nevertheless, since Ψ 1870 there appears to be a distinct, if slight, diminution in the occurrence of the disease.

UTERUS.—*Females.*—The percentage-incidence of uterine cancer has remained fairly constant since Ψ 1855, a very slight tendency to increase being perhaps discernible. In the age-35 populations of the two decades preceding 1855, the percentages recorded were considerably higher than of populations in the last half of the century; it would therefore appear that the percentage occurrence of carcinoma uteri increased in age-35 populations up to the quinquennium 1835–39, that it then gradually fell in populations of the next twenty years, and that subsequently it has remained approximately constant at a lower level with, however, a slight tendency to increase.

VAGINA.—Carcinoma of the vagina has remained approximately constant since Ψ 1835; and if any certain distinction can be made between the percentages for age-35 populations of the last twenty years and those recorded for the earlier quinquennia, a slight diminution in frequency would appear to be indicated.

VULVA.—Carcinoma of the vulva has shown a distinct though slight tendency to decrease throughout the century (Ψ).

Summary of Cancer of the Genital Tract.

A glance at Table V. will show that in populations age-35 since 1865 cancer of the male generative organs has not

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undergone any marked variations. If one exclude age-35 populations for years before 1835, in which the numbers are very few, then the maximum appears to have been attained in the age-35 populations between 1850 and 1864.

Cancer of the generative tract in women apparently rose in our age-35 populations till that of the quinquennial period 1835–39, when the maximum was reached. Amongst populations of the next forty years there is a tendency to decline, the curve being marked, however, by great irregularities and excursions on either side. Age-35 populations of the last twenty years indicate a slight tendency to increase of cancer of the generative tract.

Other Sites of Primary Cancer.

BLADDER.—*Males.*—The percentage-incidence of vesical cancer in men was distinctly higher up to Ψ 1855 than in the quinquennia succeeding that date, but from 1855 to the end of the century the figures are rather irregular.

Females.—Considerable difficulty obtains in connexion with carcinoma of the bladder in women owing to the uncertainty whether the disease is primary in that viscus, or whether it has extended from a primary focus in the uterus. The percentage occurrence, however, appears to have been lowest between 1855 and 1870 (Ψ); it then rose rapidly in the next quinquennium, but again sank, although there is discernible at present a very slight though regular tendency to increase.

BREAST.—*Males.*—The percentage-incidence of mammary cancer in males has undergone considerable quinquennial variations of a somewhat irregular nature, and no very definite information can be forthcoming as to the course taken by this form of cancer.

Females.—Breast cancer in females steadily declined from Ψ 1815 to Ψ 1844. Then the percentage rose again, from 34·8 to 40·4; and although it evinced a tendency to drop in the age-35 populations of the early part of the sixth and throughout the seventh decade, nevertheless it remained approximately constant up to Ψ 1894. There is a slight fall again in the last quinquennium (Ψ) of the century. Thus if one considers the incidence of mammary cancer in women through-

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out the century, the conclusion is forced upon one that there was at first a considerable decline, but that in age-35 populations of the last fifty years the percentage occurrence has remained approximately constant, with possibly a slight tendency to a further increase.

SKIN.—*Males.*—Primary cancer of the skin has undergone a distinct diminution in its percentage-incidence throughout the century, the lowest figures being attained in the quinquennial period Ψ 1880–84. Since Ψ 1884 there has been a slight attempt at an increase; but even in these last three quinquennia (Ψ) the figures in point of magnitude bear no comparison with those ascertained in the earlier and middle part of the century (Ψ).

Females.—On the whole there would appear to have been a diminution in the percentage-occurrence of carcinoma of the skin in women; since Ψ 1880 the figures are approximately constant.

RODENT CANCER.—*Males.*—The general tendency throughout the century has been towards a decline in the incidence of rodent cancer in males. This curve has not been an uninterrupted one throughout; thus between Ψ 1830 and Ψ 1844, a slight temporary rise is recognizable; but from Ψ 1845 the irregularities and excursions are but little marked and interfere but little with the steady downward direction of the curve.

Females.—Between Ψ 1814 and Ψ 1849 there are marked irregularities, but the great tendency is to a decrease in the percentage-incidence. Then follows a slight rise during the next three quinquennia; but from Ψ 1865 the percentage progressively diminishes.

LARYNX.—*Males.*—The percentage-incidence appears to have reached its maximum in the quinquennium Ψ 1875–79, but the decade (Ψ) preceding this is remarkable for its very low percentages. No very definite conclusions can be formed about the percentage-incidence of this form of carcinoma.

Females.—So few cases of female cancer of the larynx appear on our tables that the information obtained therefrom as to the quinquennial variations cannot be regarded as of much value. The percentage occurrence, however, appears to have been moderately constant.

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II. — CANCER AT DIFFERENT PRIMARY SITES AMONGST AGE-35 POPULATIONS CONSIDERED IN REFERENCE TO THE GENERAL MORTALITY OF THOSE POPULATIONS.

The percentage-incidence of cancer at the different sites has also been considered in relation to the total *general mortality* of the age-35 populations for the various quinquennia, and the percentages are set forth in Tables VI. and VII., which deal with males and females respectively. The conclusions which can be drawn from these quinquennial variations as to whether cancer at any particular site is or has been on the increase or decrease, agree for the most part with those already formed from a consideration of the percentage-incidence in relation to the total *cancer mortality*. Thus on investigating the percentage occurrence of cancer of the various portions of the alimentary tract, one finds that both sets of figures agree on the following points :—

1. Labial cancer in males diminished to between Ψ 1870 and Ψ 1880, and has subsequently shown a tendency to increase; cancer of the lip in women has also shown a tendency to decrease.

2. Cancer of the tongue in men has, on the whole, increased, the figures derived from Table VI. accentuating the increase more markedly than those obtained from Table III.; lingual carcinoma in females has remained more or less constant with a slight tendency to diminish in frequency.

3. Cancer of the cheek and other parts of the mouth in males has distinctly increased throughout the century (Ψ); in females a slight tendency to decline is discernible.

4. Cancer of the œsophagus has increased in males, while in females it has remained more or less constant.

5. Gastric cancer has increased in both sexes, more especially in the case of males.

6. Cancer of the colon has increased in males, while in women it increased at first, but has recently shown a tendency to decline.

7. There has been a marked increase in the incidence of rectal and anal carcinoma in both males and females.

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That these conclusions are supported by two sets of figures, viz. Tables III. and VI. in the case of males, and Tables IV. and VII. in the case of females, is strongly suggestive of their accuracy.

The tendency to an increase in the incidence of cancer of the uterus is emphasized more markedly in Table VII. than in Table IV., and further, on the evidence of the figures in the latter table, it was stated (p. 58) that in age-35 populations of the last 50 years the percentage occurrence of mammary cancer in women has remained approximately constant, with possibly a slight tendency to increase. The figures in Table VII. indicate clearly that there has been a progressive incidence of cancer of the breast in women since the commencement of the second quarter of the century.

The diminished incidence of rodent ulcer and cancer of the skin seems to be more clearly marked when the percentage is considered in relation to the cancer mortality rather than in relation to the total general mortality.

CONCLUSIONS.

From the foregoing pages it may be concluded:—

(1) That comparing healthy populations of age 35 at different periods in the nineteenth century, an increase in the mortality from carcinoma has shown itself, or is showing itself, in the case of the following organs or tracts:—

i. The alimentary tract in both sexes.
ii. Lip in males.
iii. Tongue in males.
iv. Floor of mouth and cheek in males.
v. Œsophagus in males.
vi. Stomach in both sexes.
vii. Colon in both sexes.
viii. Rectum and anus in both sexes.
ix. Uterus.
x. Breast in females.

(2) That comparing healthy populations of age 35 at different periods in the nineteenth century, a diminution in

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the mortality from carcinoma has shown itself, or is showing itself, in the case of the following sites :—

i. Lip in females.
ii. Tongue in females.
iii. Floor of mouth in females.
iv. Vulva.
v. Rodent ulcer and skin in both sexes.

(3) That the general conclusion is that comparing healthy populations of age 35 at different periods in the nineteenth century, the increase in cancer which was shown to be occurring, according to the experience of the Middlesex Hospital, is distributed more or less evenly over all the principal primary seats of the disease, and is not *markedly* associated with any one particular organ. Nevertheless it is more evident in connexion with the alimentary tract. In the case of females these points are shown graphically on p. 62 by the general parallelism of the curves for alimentary, uterine, and mammary cancer together with the actually greater height attained by the curve representing cancer of the female alimentary tract.

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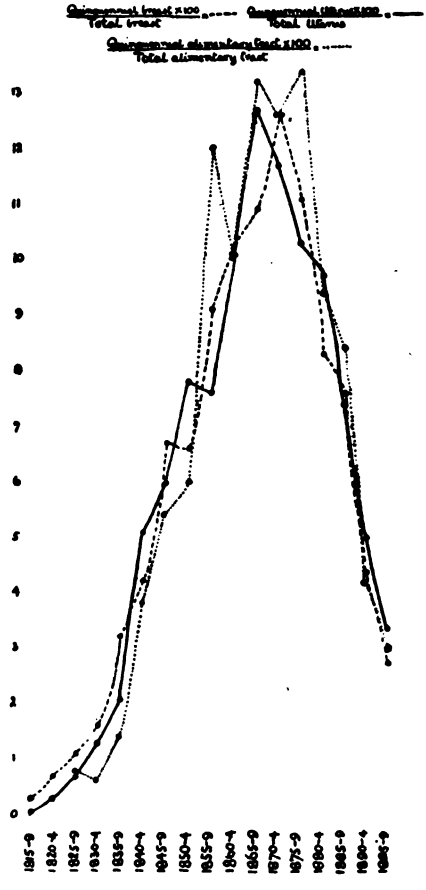
CURVES SHOWING THE QUINQUENNIAL PERCENTAGES OF CANCER OF THE FEMALE ALIMENTARY TRACT, BREAST, AND UTERUS.



NOTE.—In considering these curves it is important to remember that the descending portions are worked out on incomplete figures for a reason given on p. 48. Hence the actual values given on the descending portions of the curves are unimportant; the general parallelism, however, is indubitable.

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TABLE I.—MALES.

TABLE SHOWING THE CANCER DEATHS IN AGE-35 POPULATIONS AT THE MIDDLESEX HOSPITAL, ARRANGED QUINQUENNIALLY AND ACCORDING TO THE PRIMARY SITE OF GROWTH.

[Estimated figures are placed within square brackets.]

Years.	Lip.	Tongue.	Other parts of Mouth.	Œsophagus.	Stomach.	Colon.	Rectum and Anus.	Liver and Bile Ducts.	Pancreas.	Penis.	Scrotum.	Prostate.	Bladder.	Breast.	Skin.	Rodent.	Larynx.
1814—19	5	2	0	1	0	0	0	0	0	0	0	0	0	0	0	3	0
1820—24	5	2	0	1	1	0	0	1	0	3	0	0	0	0	0	3	0
1825—29	6	4	2	1	6	2	2	0	0	3	0	0	0	0	1	2	0
1830—34	11	3	1	4	4	1	0	1	0	0	0	0	1	0	6	3	0
1835—39	17	13	4	2	3	1	4	2	0	2	1	1	0	2	4	7	0
1840—44	11	12	5	5	11	2	7	2	1	1	1	1	0	0	4	9	1
1845—49	19	18	9	8	6	4	10	5	2	3	0	0	5	2	4	11	1
1850—54	20	28	16	12	8	4	18	8	0	8	2	2	4	2	5	10	2
1855—59	25	46	31	12	9	7	26	9	1	7	3	0	3	2	5	5	2
1860—64	31	48	37	23	14	3	24	4	0	6	8	2	1	2	3	16	5
1865—69	20 [4·5]	47 [10·2]	28 [2·9]	13 [1·0]	17 [1·3]	8 [0·3]	38 [2·7]	6 [0·3]	2 [0·2]	2 [0·8]	5 [0·1]	2 [0·8]	3 [0·5]	1 [0·2]	4 [0·5]	11 [2·1]	1 [0·3]
1870—74	16 [7·2]	62 [8·7]	36 [4·9]	20 [3·2]	29 [3·0]	10 [2·3]	34 [7·7]	8 [0·9]	2 [0·6]	5 [1·7]	3 [0·1]	1 [1·0]	3 [1·4]	4 [0·3]	4 [1·4]	9 [4·2]	1 [0·6]
1875—79	13 [13·2]	57 [18·8]	45 [13·7]	36 [10·0]	27 [6·5]	9 [3·8]	31 [15·4]	5 [3·4]	3 [1·1]	5 [3·1]	2 [0·3]	0 [1·4]	1 [1·8]	0 [0·6]	3 [3·4]	8 [7·8]	9 [1·4]
1880—84	11 [18·3]	45 [28·8]	30 [21·7]	32 [18·0]	17 [12·0]	14 [5·4]	26 [20·8]	4 [5·1]	2 [1·5]	5 [3·7]	4 [1·1]	1 [1·5]	4 [2.2]	0 [1·1]	0 [3·8]	10 [10·2]	2 [2·0]
1885—89	9 [23·4]	29 [43·8]	16 [28·5]	11 [23·2]	17 [19·1]	10 [8·2]	21 [27·4]	5 [6·0]	1 [2·0]	2 [5·1]	2 [2 5]	0 [1·5]	0 [3·2]	4 [1·7]	3 [4 5]	7 [12·8]	1 [2·9]
1890—94	2 [29·3]	17 [59 2]	5 [35·9]	8 [28·7]	11 [25·6]	2 [10·5]	12 [33·4]	1 [7·9]	1 [2·1]	3 [6·7]	2 [3·4]	0 [1·6]	2 [3·9]	0 [2·1]	0 [5·2]	2 [15·7]	1 [4·1]
1895—99	2 [32·3]	8 [67·8]	6 [40·8]	5 [31·0]	4 [29·0]	5 [11·8]	4 [39·0]	1 [9·0]	0 [2·3]	1 [8·0]	0 [5·0]	0 [1·7]	0 [4·0]	1 [3·2]	0 [5·8]	1 [17·2]	1 [4·2]

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TABLE II.—Females.

Table showing the Cancer Deaths in Age-35 Populations at the Middlesex Hospital, arranged Quinquennially, and according to the Primary Site of Growth.

[Estimated figures are placed within square brackets.]

Years.	Lip.	Tongue.	Other parts of Mouth.	Œsophagus.	Stomach.	Colon.	Rectum and Anus.	Liver and Bile Passages.	Pancreas.	Uterus.	Vagina.	Vulva.	Bladder.	Breast.	Skin.	Rodent.	Larynx.
1814—19	0	0	0	0	0	0	0	0	0	1	0	0	0	6	0	1	0
1820—24	0	0	0	0	0	0	0	0	0	5	0	1	0	12	2	0	0
1825—29	0	2	1	0	1	0	0	2	0	11	0	2	0	16	0	2	0
1830—34	0	0	1	0	1	1	0	2	0	22	0	2	0	26	3	0	0
1835—39	1	1	3	0	2	0	0	1	1	34	1	2	1	51	2	9	0
1840—44	0	3	2	2	5	1	3	5	1	82	3	7	1	67	2	3	0
1845—49	0	7	4	0	9	2	5	10	0	96	2	9	2	108	6	3	0
1850—54	1	6	2	2	9	1	11	1	0	132	3	5	2	106	1	7	1
1855—59	2	11	11	3	7	6	19	7	0	127	5	4	1	146	4	8	0
1860—64	2	3	8	2	7	6	23	7	3	167	4	12	1	161	5	13	0
1865—69	1 [0·1]	9 [0·7]	0 [0·4]	4 [0·1]	14 [0·2]	9 [0·1]	28 [1·0]	7 [0·6]	1 [0·0]	215 [2·5]	5 [0·1]	10 [0·7]	1 [0·2]	176 [6·8]	2 [0·3]	13 [1·3]	1 [0·0]
1870—74	0 [0·4]	9 [1·7]	2 [1·3]	5 [0·4]	16 [1·0]	5 [·9]	29 [3·3]	13 [1·8]	5 [0·4]	195 [10·9]	5 [0·6]	14 [2·8]	8 [0·6]	209 [23·5]	3 [1·1]	9 [3·9]	1 [0·0]
1875—79	1 [0·4]	3 [2·1]	5 [·1]	6 [0·8]	14 [4·5]	14 [2·4]	24 [8·7]	10 [4·4]	0 [0·8]	175 [31·1]	6 [1·5]	6 [5·1]	2 [1·3]	188 [52·8]	5 [2·3]	7 [5·1]	1 [0·1]
1880—84	1 [0·8]	5 [4·0]	1 [3·6]	2 [1·3]	10 [7·8]	10 [4·6]	23 [10·4]	3 [6·1]	2 [1·2]	171 [63·1]	2 [1·8]	8 [7·8]	1 [2·5]	141 [96·6]	1 [2·9]	7 [6·6]	0 [0·1]
1885—89	0 [1·0]	4 [5·8]	1 [4·5]	1 [2·5]	9 [10·5]	6 [6·1]	22 [21·0]	3 [6·9]	2 [1·8]	135 [110·0]	1 [2·7]	1 [9·3]	1 [2·8]	124 [140·0]	1 [3·3]	6 [8·2]	0 [0·6
1890—94	0 [1·0]	3 [7·8]	1 [5·0]	2 [3·1]	5 [12·7]	1 [7·2]	10 [24·6]	3 [8·1]	1 [2·2]	94 [164·1]	1 [3·9]	1 [10·2]	1 [3·0]	81 [184·7]	0 [4·2]	0 [10·4]	1 [0·7]
1895—99	0 [1·0]	1 [8·7]	0 [5·4]	0 [3·7]	4 [14·9]	3 [9·0]	7 [27·8]	0 [9·9]	1 [2·5]	62 [217·8]	1 [5·1]	4 [10·8]	1 [3·3]	50 [223·8	0 [5·0]	0 [10·6]	0 [0·7]

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TABLE III.—MALES.

TABLE SHOWING THE QUINQUENNIAL PERCENTAGES IN THE MORTALITY FROM CANCER IN AGE-35 POPULATIONS AT THE MIDDLESEX HOSPITAL.

Arranged according to the Primary Site of Growth and in relation to the total Cancer *Mortality for the Corresponding Quinquennium.*

Years.	Lip.	Tongue.	Other Parts of Mouth.	Œsophagus.	Stomach.	Colon.	Rectum and Anus.	Liver and Bile Ducts.	Pancreas.	Penis.	Scrotum.	Prostate.	Bladder.	Breast.	Skin.	Rodent.	Larynx.
1814–19	45·45	18·18	0	9·09	0	0	0	0	0	0	0	0	0	0	0	27·27	0
1820–24	31·25	12·50	0	6·25	6·25	0	0	6·25	0	18·75	0	0	0	0	0	18·75	0
1825–29	20·79	13·79	6·89	3·44	20 69	6·89	6·89	0	0	10·34	0	0	0	0	3·44	6·89	0
1830–34	28·94	7·89	10·52	10·52	10·52	2·63	0	2·63	0	0	0	0	2·63	0	15·78	7·89	0
1835–39	26·15	20·00	7·69	3·07	4·61	1·53	6·15	3·07	0	3·07	1·53	1·53	0	3·07	6·15	10·76	0
1840–44	14·47	15·79	6·57	6·57	14·47	2·63	9·21	2·63	1·31	1·31	1·31	1·31	0	0	5·26	11·84	1·31
1845–49	16·96	16·07	8·03	7·14	5·35	3·57	8·92	4·46	1·78	2·67	0	0	4·13	1·78	3·57	9·82	0·89
1850–54	13·24	18·54	10·59	7·94	5·29	2·64	11·92	5·29	0	5·29	1·32	1·32	2·64	1·32	3·31	6·62	1·32
1855–59	12·95	23·73	16·06	6·21	4·66	3·62	13·47	4·66	0·51	3·62	1·55	0	1·55	1·03	2·59	2·59	1·03
1860–64	13·65	21·14	16·29	10·13	6·16	1·32	10·57	1·76	0	2·65	2·65	0·88	0·44	0·88	1·32	7·04	2·20
1865–69	10·60	22·16	13·37	6·06	7·91	3·59	17·61	2·72	0·93	1·21	2·23	1·21	1·50	0·50	1·93	5·67	0·57
1870–74	7·81	23·82	13·78	7·81	10·80	4·15	14·07	3·00	0·81	2·26	1·04	0·67	1·68	1·45	1·82	6·48	0·54
1875–79	7·22	20·89	16·18	12·68	9·23	3·52	13·62	2·31	1·13	2·23	0·63	0·38	0·77	0·16	1·76	4·35	2·85
1880–84	8·27	20·84	11·77	14·11	8·18	5·47	13·21	2·56	0·98	2·45	1·43	0·72	1·75	0·31	1·07	5·70	1·12
1885–89	9·15	20·57	12·57	9·66	10·20	5·14	13·68	3·10	0·84	2·00	1·27	0·42	2·05	1·61	2·12	5·59	1·16
1890–94	9·36	22·79	13·23	10·97	7·94	3·73	13·58	2·66	0·92	2·90	1·61	0·47	1·76	0·62	1·55	5·29	1·52
1895–99	9·76	21·58	13·32	10·25	9·39	4·78	12·24	2·84	0·65	2·56	1·42	0·48	1·13	1·10	1·65	5·18	1·48

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TABLE IV.—FEMALES.

TABLE SHOWING THE QUINQUENNIAL PERCENTAGES IN THE MORTALITY FROM CANCER IN THE AGE-35 POPULATIONS AT THE MIDDLESEX HOSPITAL.

Arranged according to the Primary Site of Growth and in relation to the total Cancer *Mortality for the Corresponding Quinquennium.*

Years.	Lip.	Tongue.	Other Parts of Mouth.	Œsophagus.	Stomach.	Colon.	Rectum and Anus.	Liver and Bile Ducts.	Pancreas	Uterus.	Vagina.	Vulva.	Bladder.	Breast.	Skin.	Rodent.	Larynx.
1814–19	0	0	0	0	0	0	0	0	0	12·5	0	0	0	75·0	0	12·5	0
1820–24	0	0	0	0	0	0	0	0	0	25·0	0	5·0	0	60·0	10·0	0	0
1825–29	0	5·0	2·5	0	2·5	0	0	5·0	0	27·5	0	5·0	0	45·0	0	5·0	0
1830–34	0	0	1·7	0	1·7	1·7	0	3·4	0	37·9	0	3·4	0	44·8	5·1	0	0
1835–39	1·00	2·7	2·7	0	1·8	0	0	0·9	0·9	49·2	0·9	1·8	0·9	46·7	1·8	8·2	0
1840–44	0	1·4	1·04	1·04	2·6	0·5	1·5	2·5	0·5	42·7	1·5	3·6	0·5	34·8	1·04	1·5	0
1845–49	0	2·6	1·4	0	3·3	0·7	1·8	3·7	0	35·9	0·7	3·3	0·7	40·4	2·2	1·1	0
1850–54	0·3	2·06	0·6	0·6	3·09	0·3	3·7	0·3	0	45·3	1·03	1·7	0·6	36·4	0·3	2·4	0·3
1855–59	0·5	2·9	2·9	0·8	1·8	1·6	0·3	0·8	0	34·3	1·3	1·8	0·2	39·4	1·08	2·1	0
1860–64	0·5	0·6	1·8	0·4	1·6	1·3	1·8	3·9	0·6	38·4	0·9	2·7	0·2	37·2	1·1	3·0	0·2
1865–69	0·21	1·80	0·07	0·8	2·7	1·7	5·6	1·4	0·19	42·5	0·9	2·09	0·23	35·7	0·45	2·79	0·19
1870–74	0·06	1·81	0·56	0·91	2·89	1·00	5·49	2·51	0·91	35·32	0·95	2·85	1·46	39·93	0·69	2·19	0·17
1875–79	0·23	0·90	1·19	1·14	3·10	2·75	5·49	2·41	0·13	34·76	1·26	1·86	0·55	40·62	1·22	2·06	0·18
1880–84	0·29	1·47	0·75	0·54	2·91	2·39	5·47	1·49	0·52	38·42	0·62	2·59	0·57	39·01	0·63	2·28	0·01
1885–89	0·15	1·48	0·83	0·53	2·96	1·83	6·53	1·50	0·57	37·53	0·56	1·56	0·57	40·31	0·65	2·15	0·09
1890–94	0·15	1·64	0·91	0·77	2·69	1·24	5·25	1·68	0·48	39·23	0·74	1·70	0·60	40·38	0·63	1·58	0·25
1895–99	0·14	1·39	0·77	0·53	2·72	1·72	5·01	1·42	0·50	40·31	0·87	2·13	0·61	39·45	0·72	1·52	0·10

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TABLE V.

Table showing the quinquennial percentages in the mortality from cancer of (a) *the alimentary, and* (b) *the generative tract in the age-35 populations at the Middlesex Hospital. Calculated in relation to the* Cancer *mortality of those populations for the corresponding quinquennium.*

Alimentary Tract.			Generative Tract.		
Years.	Males.	Females.	—	Males.	Females.
1814–19	72·72	0	1814–19	0	12·50
1820–24	56·25	0	1820–24	18·75	30·00
1825–29	79·38	10·00	1825–29	10·34	32·50
1830–34	71·02	5·10	1830–34	0	41·30
1835–39	69·20	8·20	1835–39	6·13	51·90
1840–44	69·71	8·08	1840–44	3·93	47·80
1845–49	66·04	9·80	1845–49	2·67	39·90
1850–54	70·16	10·65	1850–54	7·93	48·03
1855–59	80·70	10·80	1855–59	5·17	37·40
1860–64	79·26	8·00	1860–64	6·18	42·00
1865–69	81·30	12·88	1865–69	4·65	45·49
1870–74	82·24	12·72	1870–74	3·97	39·12
1875–79	83·34	14·80	1875–79	3·24	37·88
1880–84	81·85	13·80	1880–84	4·60	41·63
1885–89	80·97	14·31	1885–89	3·69	39·65
1890–94	80·60	12·65	1890–94	4·98	41·67
1895–99	81·32	12·28	1895–99	4·46	43·31

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TABLE VI.—MALES.

TABLE SHOWING THE QUINQUENNIAL PERCENTAGES IN THE MORTALITY FROM CANCER IN THE AGE-35 POPULATIONS AT THE MIDDLESEX HOSPITAL.

Arranged according to the Primary Site of Growth and in relation to the General *Mortality of those Populations for the Corresponding Quinquennium.*

Years.	Lip.	Tongue.	Other parts of Mouth.	Œsophagus.	Stomach.	Colon.	Rectum and Anus.	Liver and Bile Ducts.	Pancreas.	Penis.	Scrotum.	Prostate.	Bladder.	Breast.	Skin.	Rodent.	Larynx.
1814–19	11·11	4·44	0	2·22	0	0	0	0	0	0	0	0	0	0	0	6·66	0
1820–24	7·81	3·12	0	1·56	1·56	0	0	1·56	0	4·68	0	0	0	0	0	4·68	0
1825–29	4·68	3·12	1·56	0·78	4·68	1·56	1·56	0	0	2·34	0	0	0	0	0·78	1·56	0
1830–34	5·79	1·58	2·11	2·11	2·11	0·53	0	0·53	0	0	0	0	0·52	0	3·16	1·58	0
1835–39	5·86	4·48	1·37	0·68	0	0·34	1·37	0·68	0	0·68	0·34	0·34	0	0·68	1·36	2·38	0
1840–44	3·17	3·45	1·43	1·43	3·17	0·57	1·96	0·57	0·28	0·28	0·28	0·28	0	0	1·14	2·52	0·28
1845–49	3·76	3·57	1·78	1·43	1·19	0·71	0·72	0·36	0·36	0·59	0	0	0·36	0·36	0·71	1·98	0·18
1850–54	3·55	4·98	2·84	2·13	1·42	0·71	3·19	1·42	0	1·42	0·36	0·36	0·71	0·36	0·89	1·78	0·36
1855–59	4·02	7·40	4·98	1·93	1·44	1·12	4·16	1·44	0·16	1·12	0·48	0	0·48	0·32	0·80	0·80	0·32
1860–64	4·84	7·50	5·78	3·59	2·17	0·47	3·75	0·62	0	0·93	1·25	0·31	0·15	0·31	0·47	2·50	0·75
1865–69	3·47	7·26	4·38	1·98	2·59	1·17	5·77	0·89	0·31	0·39	0·72	0·39	0·49	0·17	0·63	1·85	0·18
1870–74	3·29	10·03	5·80	3·29	4·54	1·74	5·92	1·26	0·36	0·95	0·44	0·28	0·62	0·61	0·76	1·87	0·22
1875–79	3·30	9·55	7·39	5·79	4·22	1·61	6·22	1·05	0·51	1·02	0·28	0·17	0·35	0·07	0·80	1·99	1·31
1880–84	4·30	10·84	6·12	7·35	4·26	2·85	6·87	1·33	0·51	1·27	0·74	0·36	0·91	0·16	0·55	2·96	0·58
1885–89	4·47	10·04	6·14	4·71	4·98	2·51	6·67	1·51	0·41	0·97	0·62	0·20	0·44	0·78	1·03	2·73	0·53
1890–94	4·78	11·65	6·25	5·61	4·06	1·91	6·94	1·36	0·47	1·48	0·82	0·24	0·90	0·32	0·79	2·70	0·78
1895–99	5·35	11·82	7·30	5·61	5·14	2·62	6·70	1·56	0·35	1·40	0·78	0·26	0·62	0·65	0·90	2·83	0·81

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TABLE VII.—Females.

Table showing the Quinquennial Percentages in the Mortality from Cancer in the Age-35 Populations at the Middlesex Hospital.

Arranged according to the Primary Site of Growth and in relation to the General *Mortality of those Populations for the Corresponding Quinquennium.*

Years.	Lip.	Tongue.	Other parts of Mouth.	Œsophagus.	Stomach.	Colon.	Rectum and Anus.	Liver and Bile Ducts.	Pancreas.	Uterus.	Vagina.	Vulva.	Bladder.	Breast.	Skin.	Rodent.	Larynx.
1814–19	0	0	0	0	0	0	0	0	0	2·77	0	0	0	16·66	0	2·77	0
1820–24	0	0	0	0	0	0	0	0	0	8·77	0	1·75	0	21·05	3·50	0	0
1825–29	0	2·00	1·00	0	1·00	0	0	2·00	0	11·00	0	2·00	0	16·00	0	2·00	0
1830–34	0	0	0·65	0	0·65	0·65	0	1·30	0	14·37	0	1·30	0	16·99	1·95	0	0
1835–39	0·41	0·41	1·23	0	0·82	0	0	0·41	0·41	14·05	0·41	0·82	0·41	21·07	0·82	3·69	0
1840–44	0	0·87	0·58	0·58	1·45	0·29	0·87	1·45	0·29	23·76	0·87	2·03	0·29	19·42	0·58	0·87	0
1845–49	0	1·58	0·90	0	2·03	0·45	1·13	2·26	0	21·67	0·45	2·03	0·45	24·37	1·35	0·67	0
1850–54	0·18	1·08	0·36	0·36	1·62	0·18	1·98	0·18	0	24·81	0·48	0·90	0·36	19·92	0·18	1·26	0·18
1855–59	0·34	1·87	1·87	0·51	1·19	1·02	3·23	1·19	0	21·52	0·85	0·68	0·17	24·74	0·68	1·36	0
1860–64	0·30	0·46	1·23	0·30	1·07	0·92	3·54	1·07	0·46	25·73	0·61	1·84	0·15	24·80	0·77	2·00	0
1865–69	0·14	1·31	0·05	0·55	1·92	1·23	3·93	1·03	0·13	29·51	0·69	1·45	0·16	24·80	0·31	1·94	0·13
1870–74	0·04	1·30	0·40	0·65	2·07	0·71	3·94	1·80	0·65	25·10	0·68	2·04	1·04	28·40	0·50	1·57	0·12
1875–79	0·17	0·66	0·88	0·84	2·29	2·03	4·05	1·78	0·09	25·55	0·95	1·37	0·40	29·85	0·90	1·50	0·13
1880–84	0·21	1·06	0·54	0·38	2·10	1·72	3·94	1·07	0·37	27·62	0·44	1·86	0·41	28·03	0·46	1·60	0·01
1885–89	0·11	1·07	0·60	0·38	2·14	1·33	4·73	1·08	0·41	27·21	0·40	1·13	0·41	29·22	0·47	1·56	0·06
1890–94	0·11	1·20	0·67	0·57	1·98	0·91	3·87	1·24	0·35	28·90	0·54	1·25	0·44	29·75	0·47	1·16	0·19
1895–99	0·10	1·00	0·56	0·38	1·96	1·24	3·61	1·02	0·36	29·29	0·63	1·53	0·44	28·47	0·52	1·10	0 07

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NOTE ON THREE EXPERIMENTAL INOCULATIONS OF ANIMALS.

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ALTHOUGH the experiments which are described below failed to give the result which was desired, the lines on which they were carried out were perhaps sufficiently unusual to warrant a brief note. They were based on two main principles. In the first place it was determined to inoculate the animals with as large an amount as possible of epithelium, with the idea of giving them more cells than the natural reaction of their bodies could combat, so that some at least might survive and grow; and, in the second place, healthy epithelium was to be used. The *rationale* of this depended on the view that there is no intrinsic difference at first between those cells from which carcinoma originates and the other cells of an organ, but that external circumstances of environment, food supply, or of some other nature have wrought on healthy cells to make them unaffected by the laws which control the normal growth of cells forming organs.

Three principal considerations were borne in mind in devising the technique of the experiments: (1) Of the innumerable experiments that have been conducted from time to time in an attempt to transfer new growths from one animal to another, so far failure has always attended inoculations where the animal inoculated has not been of the same species as that from which the growth was removed. More than this, it appears from the most recent experiments of Jensen, Borrel, Michaelis and others on the neoplasms of mice, that the inoculated animal must not only be of the same species, but also of the same variety. (2) In the case of squamous epithelium it is well known that "grafts" can be made to grow on a granulating surface. (3) In experiments where

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cartilage from the growing ends of fœtal bone has been introduced into the tissues of another animal a certain amount of actual growth has been observed in some instances, although the ultimate fate of the cartilage was its absorption. In short it was felt (1st) that the material to be inoculated should be epithelium, (2nd) that it should be fœtal, (3rd) that the animal used for inoculation should be identical in species and variety with that whence the fœtal epithelium was derived.

The material for inoculation was therefore derived entirely from rabbits, and was obtained in the following way: A pregnant doe was carefully watched, and immediately after birth one of the litter was killed and rapidly skinned. This skin served for experiment A. Another of the litter was killed and opened, and its entire intestinal tract was rapidly removed and slit up. This served for experiment B. The doe was killed, and a large portion of Fallopian tube was slit up and served for experiment C. In each case the material in question was introduced into the peritoneal cavity of another full-grown rabbit, through a median incision which was afterwards closed by sutures.

A.—Buck rabbit; received the entire skin of the trunk of a new-born rabbit after it had been washed in boric acid lotion. A week after the operation there was great swelling of one scrotum, and an ulcer subsequently formed, involving a considerable area of the anterior abdominal wall; this, however, completely healed up. During the time of the ulceration and after, the temperature of the animal was as a rule about ·5° Fah. below that which it had been prior to the operation. About two months later a small thick-walled abscess formed in the anterior abdominal wall and was opened. This rabbit was killed about ten months after inoculation. On examination of the body all the viscera appeared healthy. In the peritoneal cavity was a more or less globular mass about an inch in diameter, scarcely if at all fixed by adhesions. When cut across, the mass had a concentric loosely laminated appearance, and consisted of tissue almost entirely fatty in nature, with a delicate capsule outside. Microscopical examination of the mass showed that the tissue inserted had suffered the fate of all foreign bodies, first becoming encap-

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suled and then removed piecemeal by phagocytosis. The mass chiefly consisted of degenerated fibrous tissue, with here and there appearances suggesting the remains of squamous epithelial cells; some leucocytes also were present.

B.—Doe rabbit; received the intestine (which had been slit up) from a new-born rabbit just killed. The wound made for inoculation healed uninterruptedly. This rabbit died from pericarditis eleven months after the operation. No trace of the material inoculated was found when the body was examined after death. The animal was in an early stage of pregnancy at the time of death.

C.—Doe rabbit; received four pieces of slit-up Fallopian tube from another recently-killed rabbit. One of the stitches in the abdominal wound suppurated, but in a fortnight the wound completely healed. The temperature showed no unusual fluctuation. The rabbit when killed, about ten months after inoculation, was found to have a small irregular mass in its peritoneal cavity, about three-quarters of an inch long and slightly fixed by adhesions; it was seen to be whiter in section and not so fatty as the mass in rabbit A. All the viscera appeared to be healthy. Microscopically, the material found in the peritoneal cavity showed undoubted masses of epithelial cells, though they were degenerated and were surrounded by large numbers of leucocytes which formed the bulk of the mass.

Comparable with these three results, but showing a very much earlier stage in the process, are those which Mr. Fowlerton obtained in a series of experiments in which he inserted portions of malignant new growths, removed by operation from patients, directly into the peritoneal cavity of rabbits. The effects of these inoculations were investigated within a few weeks of their performance, and showed that the tissues became first of all encapsulated, and then beneath the capsule the presence of a zone of leucocytes indicated the gradual removal of the foreign substance by phagocytosis.

Though the experiments here recorded are only three in number, they are given because of the principles on which they were done, and because they show once more the uniformity of the reaction of the animal body to foreign substances lodged within it, whatever their source may be.

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THE RELATION OF ELASTIC TISSUE TO CARCINOMA.

By G. T. WRENCH, M.D., B.S.LOND.

THE following research was undertaken in order to determine whether elastic fibres ever form an essential constituent of the stroma of carcinomata.

I.—PREVIOUS WORK.

Melnikow-Raswedenkow[1] found there was no increase of elastic tissue in tumours, the original elastic tissue of an organ being only mechanically influenced by the tumour element. In chronic inflammation he found there was often abundant multiplication of elastic fibres.

Fischer[2] found the stroma of carcinomata of the breast generally free of elastic fibres. In some cases elastic masses were present, surrounding clumps of carcinomatous cells, but more frequently enveloping small vessels or ducts with a thick mantle.

White,[3] dealing with the distribution of connective tissue in new growths, found a great quantity of elastic fibres in some cases of carcinoma mammæ. He thinks new formation probably occurs.

Williams[4] examined 37 cases of carcinomata, amongst which he mentions 3 cases of carcinoma of the liver in which new formation of elastic fibres was evident. One of these he considered to belong more to the province of cirrhosis than carcinoma. He does not say whether these cases were primary or secondary. Neither does he say whether any other cases exhibited new formation of elastic fibres. He concludes that when stroma of carcinoma is itself of new formation, it is usually free of elastic tissue. Elastic fibres of new formation may rarely occur in stroma, and are then fine in quality and small in number. When such new

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formation takes place, it takes place in tumours with a large amount of connective tissue or in connection with pre-existing elastic elements.

Hektoen and Riesman[5] in their text book of Pathology say that it is highly probable that certain tumours, both benign and malignant, ectodermic and mesodermic, are capable of elaborating new elastic tissue during their growth. When the stroma is formed from the framework of the parent tissue, elastic tissue exists as it originally did, apparently in an unaltered qualitative and quantitative condition.

II.—METHODS.

After experimenting with various stains (orcein, picrocarmine, etc., with many modifications) Weigert's stain as advised by Fischer[2] was finally adopted. All the sections, which were cut from paraffin blocks, were submitted to absolute alcohol for one hour after staining in Weigert. Though it is open to question if so long an exposure to absolute alcohol be fundamental, it is useful, in that it ensures a similarity of method between different observers.

The majority of specimens were subjected to both the following methods, and the slides of each compared.

A.—1. Lithio-carmine (dilute) 15 minutes.
2. Wash in 1% HCl.
3. Weigert's stain for not less than one hour.
4. Absolute alcohol one hour.

B.—1. Weigert's stain as above.
2. Absolute alcohol as above.
3. Van Gieson's stain 40 seconds, followed by picric water, picric absolute alcohol, and xylol.

Some fresh sections were stained with picrocarmine. They differed from the fixed sections in that the continuity of the elastic tissue was preserved, whereas in the fixed sections the tissue is, as a rule, broken into fragments and bits of fibre.

The diagnosis as regards carcinoma had been made from slides stained by hæmatoxylin and eosin. After the research was ended all the specimens were re-examined for confirmation.

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III.—SOURCE OF MATERIALS.

i. Ten specimens of primary spheroidal cell carcinoma of breast.
ii. Forty-seven metastases from the above.
iii. Two columnar cell carcinomata of the breast becoming transitional with two metastases.
iv. Two spheroidal cell carcinomata of the pancreas with four metastases.
v. Four squamous cell carcinomata of the lip with five metastases.
vi. Three transitional cell and two columnar cell carcinomata of the rectum with eight metastases.
vii. About 60 specimens from normal and diseased tissues for the sake of interpreting similarities or differences of phenomena that appeared in the slides of carcinoma.

IV.—DESCRIPTION OF MICROSCOPIC APPEARANCES.

(i) *Primary Spheroidal Cell Carcinomata of the Breast.*

(10 specimens.)

In these primary breast carcinomata portions for examination were taken from the growing edge. In five cases skin was included. In all ten cases tissues normally containing elastic fibres were present, *e.g.* corium, vessels, ducts, etc. But where the carcinoma was most removed from such sources, whether it approached in character to a pure cellular growth or was densely scirrhous, elastic fibres were either absent or in scarce and isolated shreds. The effect of carcinoma upon the elastic tissue of the corium and subcutaneous tissue was mechanical, and although the elastic fibres offer greater resistance than the stout fibrous bundles of the corium, yet it is pushed to one side, broken up, and eventually disappears. In one section an elongated mass of dense elastic tissue had been driven up in a compressed barrier against the epidermis comparable to the way in which carcinoma of the lung may sweep pigment into a heap before it. But as a rule

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the carcinomatous cells freely invade the elastic web and break it up into bits and shreds, which at first irregularly occupy the stroma, but eventually disappear.

With regard to the elastic tissue that surrounds the blood-vessels and lactiferous ducts of the breast, a different sequence obtains. In the sections, four cases, in which these structures were best shown, a large quantity of elastic fibres occurred, so that their mass could be detected by the naked eye.

The reason of this great quantity is really a subject of special investigation, as it does not influence the question of new formation of elastic fibres in the stroma of carcinoma. A few specimens were cut and investigated with a view to throwing light on the reason of this great quantity of elastic tissue enveloping ducts and vessels.

Jores[7] found a great increase in arterio-sclerosis, and this would explain the increase about the vessels but not about the ducts.

It was not due to ulceration, for it occurred in two breast carcinomata from the operating table in which no ulceration had occurred.

A comparison with four cases of chronic mastitis did not warrant the view that it was due to chronic inflammation.

Three cases of fibro-adenoma showed no such great quantity as is found in carcinoma.

Of five undiseased breasts, two, from women æt. 41 and 53 respectively, showed irregular and lumpy masses of elastic tissue round ducts and vessels, comparable to that occurring in carcinoma, but not equal to it in amount.

White[8] compared one carcinoma of the breast and the unaffected breast tissue in which it occurred. He found less elastic tissue amongst the carcinoma than in the unaffected breast.

In the present investigation a fresh carcinoma of the breast was obtained from an operation. Four specimens were taken, the first from the scirrhous centre, the second from the periphery, the third from the breast just beyond the edge of growth, and the fourth yet further from the growth in un-diseased breast tissue. All four specimens showed lactiferous ducts. Those in the first two specimens exhibited dense and lumpy increase of elastic fibres around and about them; those

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in the last two specimens, beyond the range of carcinoma, showed no such increase.

From the above it appears that under certain as yet undetermined conditions an overgrowth of elastic tissue takes place around bloodvessels and ducts in mammary carcinoma. Owing to this great quantity of elastic tissue in the walls of the vessels and ducts, it is not surprising to find elastic tissue abundant in the stroma of the adjacent carcinoma, and in some few places, doubtless by coincidence, it definitely surrounded carcinomatous alveoli. But generally it was so irregularly disposed in the carcinomatous stroma that it could probably be looked upon as waste and useless material. Often strands of elastic fibres were seen, due in all probability to the section cutting the thick elastic envelope of a duct or vessel without including its lumen. When by pressure of the new growth the lumen was obliterated a roundish mass of elastic tissue, much of which was granular, was left.

Still, in all cases the rule held, that the portions of carcinoma furthest removed from such sources of elastic tissue were free of elastic tissue. With regard to the disappearance, a search was made in selected slides for phagocytic phenomena, but none was seen.

(ii.) *Metastases from Primary Spheroidal Cell Carcinomata of the Breast.*

(47 specimens.)

Of these 47 specimens, 9 occurred in the liver, an organ free of elastic fibres except capsule and portal systems, 6 in the axillary tissues, which contain plenty of elastic tissue from vessels, etc., 4 in the kidneys, which normally contain no elastic tissue except in the capsule, and 6 in the lungs, which have a large amount of perialveolar and peribronchiolar elastic tissue. The remaining 22 were variously distributed in glands and other organs.

In all these metastases, the purer the carcinomata and the further removed from normal sources of elastic fibres, the freer was their stroma of elastic fibres. In the liver and kidney, organs in which the glandular elements are normally completely free of elastic tissue, and hence afford no normal

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sources of elastic to the carcinomatous stroma, this stroma was itself completely free of elastic fibres.

(iii) *Two Columnar Cell Carcinomata of Breast becoming transitional with two Metastases in the Axillary Tissues.*

(4 specimens.)

In the normal breast the columnar cells lining the lactiferous ducts are encircled by the elastic fibres in the walls of the ducts. The spheroidal cells of the acini are not encircled with elastic fibres. In these specimens, although the columnar cell carcinomata were in tubular arrangement, no elastic fibres encircled them. As usual, a few occasional and scattered pieces of elastic tissue were to be seen in the sections, but they had no continuity and were regarded as remnants from pre-existing tissue.

(iv) *Two Spheroidal Cell Carcinomata of Pancreas with four Metastases.*

The specimens showed the stroma of the carcinoma to be free of elastic fibres.

(v) *Four Squamous Cell Carcinomata of the Lip with five Metastases.*

Three of the metastases occurred in the submaxillary gland, an organ which has abundant elastic tissue. The rule held good, however, that the further the growth was from sources of elastic tissue, the freer was its stroma. The other two metastases occurred in lymph glands, and their stroma was free of elastic tissue.

The four primary growths showed a few fine fibres of elastic tissue divided from the skin.

(vi) *Three Transitional Cell and two Columnar Cell Carcinomata of the Rectum with eight Metastases.*

The wall of involuntary muscle of the rectum normally contains elastic fibres between the muscle bundles. In the primary growths, the carcinoma could be seen invading this muscular layer, which formed wide bands between large groups of carcinomatous cells. These bands all contained

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elastic fibrils in fair quantity. It was notable that where the nuclei were long, like those of involuntary muscle, there were also elastic fibrils. On the other hand, where the stroma was slighter and no long nuclei could be seen, there elastic tissue was absent.

In one of the columnar cell carcinomata of the rectum, the carcinoma which invaded the muscular coat seemed to have attracted to itself the elastic fibrils of that coat, for the tubules were surrounded by encircling elastic fibrils, so as to present the appearance of an elastic wall to the tubules. This only occurred where the muscular wall was invaded by the carcinomata. Elsewhere the carcinomatous tubules had no elastic fibres round them.

Of the eight metastases, three were in the liver, two in the lung, and three in glands. No new formation of elastic tissue was seen.

Hence in ninety-one specimens of carcinomatous growth, the rule was that the carcinomatous stroma was free of elastic tissue, except that left from pre-existing sources. No new formation of elastic tissue occurred in the stroma.

There is some evidence to show that an actual increase of elastic tissue does occur around the lactiferous ducts and blood vessels in carcinomatous breasts.

V.—THE RÔLE OF ELASTIC TISSUE IN ENCAPSULATION.

The writer has not been able to find any statement on the share of elastic fibres in encapsulation.

Weigert's stain showed the existence of elastic fibres in the partial capsules of degenerated carcinomata in four specimens. In one specimen a degenerated mass of distinct carcinoma of the kidney had a dense capsule with abundant and orderly disposed elastic fibres in it. As a contrast in the same case, a similarly degenerated mass in the uterus showed a thick capsule without elastic fibres. As regards the occurrence of elastic fibres in the capsules of neoplasms or foreign bodies, it was found in the capsule of a kidney infaret, around a piece of cartilage that was left in the midst of a bone metastasis otherwise free of elastic tissue, in the capsule of a thyroid

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adenoma, in very fine and few threads in the capsules of two fibro-adenomata of the breast, and was absent in a third Even in the third fibro-adenoma there was some hint of elastic threads in the process of formation.[7]

It is present in definite layers in the capsule of the liver, kidneys, testes, ovaries, adrenals, etc.

VI.—ELASTIC TISSUE AND PRIMARY CARCINOMA OF THE LIVER.

The relation of elastic tissue to primary carcinoma of the liver is considered separately, for the study throws some light on the so-called carcinoma with cirrhosis. For comparison, twelve secondary carcinomata of the liver were examined. In all cases the stroma showed a small-meshed arrangement, roughly speaking 10 to 40 meshes occupying a field of the microscope under a ½-inch objective and No. 4 eyepiece. In all cases this stroma was free of elastic tissue. One of these metastatic nodules occurred in a cirrhotic liver. Its stroma was small-meshed and free of elastic tissue. A few shreds of the connective tissue bands of the liver with elastic tissue were however left in the carcinoma. The carcinoma had made no use of the pre-existing connective tissue of the liver, as it did in two of the primary carcinomata with cirrhosis. Williams [4] describes one case of carcinoma of the liver—he does not say whether it was primary or secondary—thus: "The acini were very large and the connective tissue septa between them broad, with numerous elastic fibres. The resemblance to the newly formed fibrous tissue seen in cirrhosis of the liver was marked in this specimen. In a case of cirrhosis carcinomatosa, elastic fibres were abundant in the connective tissue bands, but there were no more in the regions occupied by the tumour than in other parts of the liver. This case probably belonged more to the province of cirrhosis than carcinoma."

In the present investigation four cases of primary carcinomata of the liver were examined. For two of them I am indebted to the kindness of Dr. Rolleston. These four cases will be described separately. Three were instances of carcinoma with cirrhosis.

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1. MIDDLESEX HOSPITAL CASE. No. 1. 1905.—This case showed a large primary mass of spheroidal cell carcinoma in the right lobe of the liver, with metastatic hepatic nodules in the rest of the liver. There were no metastases elsewhere, and the liver itself was not cirrhotic.

Microscopically both primary and secondary growths showed small-meshed, delicate stroma free of elastic fibres.

2. MIDDLESEX HOSPITAL CASE. No. 177. 1904.—Carcinoma with cirrhosis. No metastases. Three specimens of this case were examined microscopically. The first specimen showed a broad, wide-meshed stroma, many of the meshes being bigger than the microscopic field under a ½-inch objective and No. 4 eyepiece. The meshes were filled with liver cells or carcinomatous cells. The stroma, which was identical with that of cirrhosis of the liver, like it contained abundant fine fibrils of elastic tissues. These fibrils are also similar in appearance to those seen in Glisson's capsule.

The second specimen showed different appearances; for delicate small-meshed stroma was present, roughly twenty to forty meshes in the field. This stroma was free of elastic tissue. A fair quantity of broad, large-meshed stroma containing elastic fibres was left, but it was in many cases invaded, broken up, and scattered by carcinomatous cells.

The third specimen showed a pure, small-meshed spheroidal cell carcinoma free of elastic tissue.

This case showed well a phenomenon also seen in other specimens, namely a small-meshed carcinoma filling the lumen of a vein or duct, and hence encircled by elastic tissue. It is notable, as regards the partial origin of stroma from the adventitia of vessels and ducts, that whereas this intraluminar stroma was quite free of elastic tissue, similar stroma immediately external to the vessel contained elastic fibrils derived from the adventitia.

3. ST. GEORGE'S HOSPITAL CASE. No. 316. 1900.—This case was reported by Dr. Rolleston as "Carcinoma in a Cirrhotic Liver," in Path. Soc. Trans., 1900. Sections stained specifically showed a wide-meshed stroma containing abundant fine fibrils of elastic tissue. Some of the meshes were filled

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with spheroidal cell carcinoma, some with fatty liver cells. There was no small-meshed stroma.

4. St. George's Hospital Case. No. 374. 1900.—The post-mortem examination showed this to be a case of primary growth in the left lobe of the liver, which presented a uniform white mass, little liver tissue remaining; secondary hepatic nodules were present in the right lobe of the liver, with nutmeg liver between them.

The section was from the primary mass. It showed spheroidal cell carcinoma with dense, small-meshed stroma. The number of meshes seen in the field depended on the density of the stroma. In places thirty to forty meshes could be counted, in other places the stroma was so dense as to occupy the whole field to the exclusion of the carcinoma. There was no elastic tissue in any of this stroma.

VII.—SUMMARY OF CONCLUSIONS.

i. The small-meshed intra-alveolar stroma of carcinoma, whether primary or secondary, is devoid of newly formed elastic tissue, except in the neighbourhood of vessels or ducts.

ii. The stroma of primary carcinoma of the liver is of at least two varieties.

a. Small-meshed stroma, delicate or dense (scirrhous), free of elastic tissue.

b. Large-meshed stroma containing abundant elastic tissue and indicating a pre-existing cirrhosis.

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MALIGNANT DISEASES OF THE BREAST: A STATISTICAL STUDY OF THE RECORDS OF THE MIDDLESEX HOSPITAL.

By P. CAMPICHE, M.D. (LAUSANNE), M.R.C.S., L.R.C.P.,

AND

W. S. LAZARUS-BARLOW, M.D., F.R.C.P.

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I.—INTRODUCTION.

The scope of the present Paper is to investigate the pathological and clinical aspects of malignant disease of the breast, taking as the sole source of information the material accumulated at The Middlesex Hospital since the middle of the eighteenth century.

The number of available observations is greater than is generally found in papers on the same subject. The largest number of cases hitherto dealt with—and that in a collective report—has been 1,842.[1] The present communication is based upon 1,976 cases. Of course, all the notes are not equally valuable, but compared with figures of corresponding magnitude, *e.g.* those of the great German "Krebszählung," of

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1902, which bears upon some 12,000 cases of all varieties of cancer throughout Germany (Hirschberg[2]), the records of The Middlesex Hospital possess a great advantage. For the present enquiry, instead of being compiled from elements of information drawn from all parts of a huge country, and necessarily looked at in different lights by the different practitioners who reported them, deals with a quite homogeneous mass of facts, accurately observed and recorded by a small number of expert medical men, whose connection with one and the same institution gives a peculiar unity to their methods.

In the year 1882 Mr. Nunn,[3] at that time Surgeon to The Middlesex Hospital, and in 1894 Mr. Roger Williams,[4] formerly Surgical Registrar, published the results of their experience on the same subject. The fact that at least ten years have elapsed since the last-mentioned report, and that during the same period the actual number of amputations of the breast performed in The Middlesex Hospital has averaged over fifty-five per annum, is sufficient excuse for a third monograph. Moreover, since 1900, histological examination of all specimens has been carried out with especial care, and this enables us to distinguish more clearly from Carcinoma all cases of Sarcoma, and possibly most cases of Endothelioma.

II.—GENERAL STATISTICS.

Taking all cases (carcinoma and sarcoma) since the year 1747 we find that the proportion of primary malignant disease of the breast (1,976 cases) to malignant growths of all organs of the body (8,955 cases) is 22·07 per cent.

In this percentage malignant disease of the female breast (1,950 cases) is 21·78 per cent., and that of the male breast (26 cases) is 0·29 per cent. During the same period (1747 to 1903 inclusive) the number of in-patients admitted to the Hospital was 126,843, giving the proportion of all patients suffering from malignant disease of the breast to in-patients admitted for all causes as 1·56 per cent. Dealing with females alone, malignant diseases of the breast constitute 35·29 per cent. of all malignant disease (5,526 cases); in other words, in females one case in every three of malignant

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disease affects the breast.[5] In males, the corresponding figures are 0·95 per cent. malignant disease of the breast to malignant disease of all organs (2,746 cases); hence, in males, cancer of the breast constitutes about one case in every hundred cases of malignant disease.

Taking the entire series of cases from 1747 the relative frequency in the two sexes is, according to The Middlesex Hospital records, as 75 to 1. This ratio is sensibly higher than those given by Roger Williams (117 to 1) and Bryant (101 to 1). But the above figure (75 to 1) is doubtful inasmuch as there is reason to believe that before the year 1858 many cases of female cancer actually admitted to the Hospital were entirely unrecorded; it must, therefore, be considered as only approximate.

To obtain more reliable information on certain points (*e.g.* pain, relation of primary to secondary disease, sarcoma, etc.) it is advisable to confine attention to the notes which begin in 1858. By doing this we eliminate the greater number of doubtful cases in the Records. Much care has been taken in reference to those cases in which recurrence after operation is recorded, in order to avoid counting twice or more times the same patient. Making these corrections we have at our disposal (from 1858 to 1903 inclusive) 1,643 cases of malignant disease of the breast in both sexes, of which 1,625 are females and 18 males.

We immediately notice that according to these more recent figures, the relative proportion of malignant disease of the breast in the two sexes is 90·28 females to 1 male, which is nearer the figure generally accepted by other authors than 75 to 1.

Sarcoma.—This pathological condition is first mentioned in the Registers of The Middlesex Hospital in 1865. From 1858, 43 primary sarcomata of the breast (1 in a man) and 2 secondary sarcomata are recorded. Thus in females primary sarcoma of the breast is to total malignant disease of the breast as 1 to 46, giving a percentage of 2·2 (Roger Williams, 3·9 per cent.). In the case of males the figures are too small to be of value, but one case of sarcoma occurred amongst 18 of malignant diseases of the breast.

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The Relation of Malignant to Non-Malignant Disease of the Breast.

TABLE I.

Table showing the number of Admissions for (a) *Malignant Disease*, (b) *Non-Malignant, and Inflammatory Diseases of the Breast between the years* 1892 *and* 1903 *inclusive.*

YEAR ...	1892.	1893.	1894.	1895.	1896.	1897.	1898.	1899.	1900.	1901.	1902.	1903.
Cases of Malignant Disease	58	38	52	50	52	66	60	58	77	63	64	70
Percentage of Total Mammary Disease.	77·3	74·5	61·9	58·8	62·7	70·2	73·2	71·6	72	70·5	68·8	67·9
(*a*) Inflammatory Diseases	6	6	13	10	15	14	7	8	13	6	6	12
(*b*) Non-malignant Growths	11	7	19	25	16	14	15	15	17	20	23	21
Total Cases of Non-malignant Disease.	17	13	32	35	31	28	22	23	30	26	29	33
Percentage of Total Mammary Disease.	22·7	25·5	38·1	41·2	37·3	29·8	26·8	28·4	28	29·5	31·2	32·1

According to this table, at The Middlesex Hospital primary malignant growth constitues on an average 69·1 per cent. of all varieties of diseases of the breast. Of the 30·9 per cent. contributed by other conditions, inflammatory changes account for 11·3 per cent., and non-malignant tumours account for 19·6 per cent. The relative constancy of these proportions throughout the series of years is remarkable.*

In the foregoing paragraphs the selection of cases of sarcoma from the total series of malignant growths depends upon macroscopic evidence only. Unfortunately microscopic evidence is only available since the year 1900. Of late years a further group, viz., endothelioma, has come to be recognised. Taking only cases of malignant disease between the years 1900 and 1904, inclusive, the following per-centages, in each case dependent upon microscopic examination alone, are obtained :—Carcinoma, 81·6 per cent.; sarcoma, 7·7 per cent.; endothelioma, 10·6 per cent. Consideration of mammary growths on the basis of histological characters only is reserved for Section VI.

* These figures correspond closely to those given by Roger Williams : malignant growths 81·6 per cent. (77·7 per cent. cancers, 3·9 per cent. sarcomata); non-malignant growths, 18·4 per cent., of which 2·7 per cent. were "cysts."

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III.—CARCINOMA OF THE BREAST IN FEMALES.

(A) Pathological Anatomy.

Site of Appearance of the Growth.

Primary carcinoma.—In 1010 cases the site at which the growth first appeared was given. These were grouped in different ways, and their combination in one series without re-arrangement is impossible. In 491 cases the distribution was as follows:—

Superior and outer quadrant . . .	275 cases
Superior and inner ,, . . .	102 cases
Inferior and outer ,, . . .	76 cases
Inferior and inner ,, . . .	38 cases

In 319 cases the distribution was as follows:—

Superior part of breast	118 cases
Outer ,, ,, ...	83 cases
Inferior ,, ,, ...	71 cases
Inner ,, ,, ...	47 cases

Further, in 123 instances the primary nodule was central, beneath the areola, and in 77 it is said to have been at the nipple.

From these figures it appears that the share of the centrally situated growths is 12·2 per cent., and of those with mamillar site is 7·6 per cent.

For the peripheral growths we shall adopt the denominations of the first series given above, since the terms "superior and outer," "superior and inner," etc., correspond better to the clinical facts than the others. If we then reduce the 319 cases of the 2nd series to terms of the 1st, we obtain for this series the following figures:—

Superior and outer quadrant . . .	179 cases
Superior and inner ,, . . .	66 cases
Inferior and outer ,, . . .	49 cases
Inferior and inner ,, . . .	25 cases

Adding these to the 491 cases of Series 1, we get the following

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distribution of 810 cases with the primary site in the periphery of the breast :—

Superior and outer quadrant . . .	454 cases
Superior and inner „ . . .	168 cases
Inferior and outer „ . . .	125 cases
Inferior and inner „ . . .	63 cases

Thus the percentage distribution of the 1010 cases is as below (Table II.).

TABLE II.

Table giving the Percentage Occurrence of Primary Carcinoma of the Female Breast, arranged according to the Site of Growth.

Beneath nipple (central) . . .	12·2 per cent.
In nipple	7·6 „
Superior and outer quadrant . .	44·9 „
Superior and inner „ . .	16·7 „
Inferior and outer „ . .	12·4 „
Inferior and inner „ . .	6·2 „

Outlying nodules.—Apart from the cases already mentioned, instances are recorded of carcinoma beginning quite outside the mamma, either in the axillary tail of the breast (10 cases), or in an outlying lobule on the sternum (2 cases).

Site of secondary carcinoma.—The amount of information given in the Hospital Records concerning the site of mammary carcinoma *secondary* to carcinoma of the other breast is very scanty, for owing to the simultaneous and generally widespread diffusion of cancer in these cases to the skin, special details are but rarely given. In 13 instances, however, of the total of 137 cases in which secondary growths were noted in the mamma, the site of the metastases is plainly stated. It was once central, once in the nipple, once in the superior and inner quadrant, and 10 times in the superior and outer quadrant. Though small, these figures support those obtained for primary disease, and indicate that the upper and outer quadrant of the breast is more closely associated with the occurrence of cancer than other parts of the organ.

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Number of initial nodules.—As a general rule cancer of the breast begins definitely at one point. In a certain number of cases, however, the occurrence of multiple primary centres appears to be possible. In one of the Middlesex cases the patient definitely asserted that she noticed several discrete nodules from the very beginning of the disease in the same breast and at the same time. This being a patient's statement cannot be received with the same amount of credence as definite information dealing with the state on admission. Besides the above case 14 instances are recorded (8 in the right breast, 6 in the left) where two or several nodules were present in different parts of the breast at the time of admission. The situations were most various—generally the nodules were peripheral. With regard to the previous history of these nodules, some patients thought that they appeared simultaneously, others were not so positive. There is no means of determining whether one nodule appeared before the others, *i.e.*, whether certain of them were secondary, but in view of the small number of recorded cases, it is not impossible that they were instances of pluricentric growths in the sense of von Hansemann.[6] Practically the rule may be adopted that carcinoma of the breast is of unicentric origin.

The side affected.—Regarding the side affected information is given in 1,512 cases. Of these, primary carcinoma involved the left breast in 777 cases, out of which 64 secondarily involved the right mamma. Primary carcinoma of the right breast obtained in 735 cases, out of which 73 secondarily involved the left mamma; thus, in 137, or 9 per cent. of the cases, the mamma was the seat of secondary cancer, the primary growth being situated on the opposite side.* The records of The Middlesex Hospital therefore confirm the opinion that is generally held, that the left breast shows a slightly greater liability to cancer than the right.

A point of great interest lies in the fact that although the left breast is more commonly the seat of cancer, yet secondary nodules in a breast are more frequent when the right gland is the seat of growth. Probably this depends upon a different

* According to Roger Williams this condition obtains in 18·1 per cent.; according to Török and Wittelshoefer[7] in 9 per cent. of cases.

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lymphatic distribution for the two breasts. If drainage of lymph towards the left is greater than towards the right thoracic duct, the peculiarity noted above is easily intelligible.

In the 137 cases which have been described where growth occurred in both breasts it is fairly certain, from the presence of multiple skin nodules over the thorax before the second mammary growth appeared, that one had to deal with cases of metastasis. Nevertheless, the point is not definite; on the contrary, it is possible that some of them were instances of double primary growth.

In the case of mammary carcinoma that is clearly secondary, the growth appears in the second breast, on an average, 3 years after the onset of the primary disease was noticed. This statement is derived from an examination of 35 cases in which the point was recorded.* The interval between the invasion of the two breasts may, however, be much longer than is indicated by an average of 3 years. Thus instances are recorded in which the interval was 7 years, 12 years, and 15 years.

A total of 20 patients were *on admission* suffering from carcinoma of both breasts, no other organ being primarily affected, so far as could be determined. This variety of case, excepting for an isolated example in 1896, totally disappears in recent years. It only occurs in patients who have waited an inordinate length of time before seeking surgical advice.

With regard to the question whether certain of the cases were examples of independent primary growths in the two breasts, those cases are of greatest importance in which either (*a*) the growths were seen simultaneously in both breasts, or (*b*) were separated by a very long interval. Reference to the first group has been made in the last paragraph. With regard to the second, it is always clear on examining the record that there has been a continuous formation of cutaneous nodules between the time of the appearance of the growth in one breast and its appearance in the other. Not a single *indubitable* instance of primary cancerous growth originating separately in both breasts, either at the same time or with an intervening period of immunity from growth, is recorded at The Middlesex Hospital.

* According to Gross the interval is 29·8 months.

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Primary carcinoma of the breast conjoined with primary carcinoma of another organ in the same individual are recorded in the following instances:—*

(1) Left breast, rodent cancer of eyelid.
(2) Left breast, rodent cancer of nose.
(3) Breast ? side, rectum.
(4) Breast ? side, cervix.
(5) Left breast, cervix.
(6) Left breast, vulva.
(7) Left breast, rectum (site of earliest growth).

In cases 1 to 6 the diagnosis was as clear as possible, apart from microscopic examination. In the 7th case it is somewhat doubtful whether the mammary growth which developed later was not secondary.

Character of the primary focus of growth.—It is regrettable that the clinical notes afford insufficient information on certain points, *e.g.* hardness, softness, presence of cysts, etc. For this reason they will be left entirely on one side; from this point of view such remarks as are possible will be made when dealing with the histological portion of the subject.

Ulceration.—In order to determine the average time of appearance of the ulcerative process, the time during which the breast was ulcerated was subtracted from the total duration of the disease. By this method it was found (for a series of 53 cases from 1897 to 1903) that ulceration of the skin appears on an average 2 years and 5 months after the first signs of breast disease have been noticed. In two other series of patients with ulcerated breasts on admission (one at the beginning, the other at the end of the period 1858 to 1903), the date of the onset of ulceration could not be calculated, but the disease had lasted 2 years and 5 months and 2 years and 10 months respectively when the patients first came to the Hospital. These three sets of figures corroborate one another well.

From 1,643 cases of mammary growth since 1858, after elimination of sarcoma, and growths affecting males, 1,581 cases remain. Of these 576, or 36 per cent., *i.e.* a little over

* The subject of multiple primary growths was discussed by Young in Archives of the Middlesex Hospital, vol. iii., p. 165.

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one-third, were ulcerated. In recent years this proportion has been altered. From 1897 to the end of 1903 (leaving aside six cases in which ulceration developed after an operation), out of 441 cases of carcinoma of the female breast, 95, or 22 per cent., were ulcerated on admission. This shows a difference of 14 per cent. in favour of the later years of the century.

Out of the total of 576 cases with ulcerated carcinoma, pronounced hæmorrhage took place in 30 instances.

Although, as the foregoing figures show, there is a greater tendency at the present day for patients to seek surgical treatment before the onset of ulceration than formerly, yet the fact that 22 per cent. of all cases are ulcerated on admission shows that ulceration, as such, plays an extremely important part in inducing them to seek relief. This is well borne out by considering the size of growths on admission. Bearing in mind the advance of education and the introduction of anæsthesia and of antiseptics, one would *a priori* expect that the size of growths on admission of patients would be smaller than formerly. As will be seen in the following paragraph this is far from being the case.

Size of growths on admission.—It is, of course, impossible to adopt a definite standard measure for the dimension of a carcinomatous tumour of the breast, but if we classify as "small," growths recorded as being the size of a "walnut," "pigeon's egg," "chestnut," etc.; as "large," those described as the size of "hen's egg," "tangerine or small orange," "cricket-ball"; and as "very large," the tumours compared to a "child's head," a "Rugby football," an "ostrich egg," etc., we find no great differences between the patients of the middle of the last century and those at the present time. The instances of "very large" growths are not quite so numerous as before, though they have by no means disappeared. But it is surprising that tumours of "large" size, though not in a majority, are still very frequently first seen on admission. How great a diminution of cancer mortality could be brought about if patients were always radically treated while the growth was still "small," it is impossible to say; but a marked improvement might be anticipated.

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Retraction of nipple.—As to the value of retraction of the nipple for diagnosis, this sign is recorded as present in 417 cases, *i.e.* in 26 per cent. of all cases. So far as positive retraction is concerned this point seems to have been accurately noted even in the early years of our series. On the other hand it is rare for statements to appear that the nipple was "normal" or "not retracted"; hence for a large number of cases there is no record on this point. It is impossible to assume that in all of these there was no retraction, and this may easily account for the difference between the figure given above, and those of other writers (*e.g.*, Gross, cited by Williams, 52 per cent.).

In considering the question whether retraction of the nipple bears a special relation to the site of growth, attention was directed to the co-existence of this condition with growth at a central or a mamillar site. Amongst the 417 cases of retracted nipple were found 46 cases of central and 28 of mamillar growth. These give percentages of 11 per cent. and 6·7 per cent. respectively, figures differing so slightly from the 12·2 per cent. and 7·6 per cent. which represent the relative tendencies of growths to affect the centre of the breast and the nipple (cf. p. 87) that no especial relationship in this direction seems to obtain. The probability that retraction of the nipple will occur is as great when the growth is peripheral as when it is central or mamillar.

With regard to the question whether retraction of the nipple is ever the first recognisable sign of disease of the breast, a single example is recorded where the retraction first appeared six years before any definite evidence of disease manifested itself in the breast. As a rule it is preceded by other phenomena, *e.g.*, tumour or pain; but of 500 records since 1894, especially examined with reference to the character of the "first symptom," retraction of the nipple was specifically stated to have been the first sign in 19, *i.e.* 3·8 per cent. (cf. p. 105).

Paget's disease of the nipple as a precursor of mammary growths.—Paget's disease, though described in 1874, finds its first example in a case at The Middlesex Hospital in 1884. Between 1884 and 1903 only six cases were recorded. The

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total number of cases of cancer of the female breast in that period being 941, this gives a percentage of 0·64 per cent., which is less than the figures given by Gross (1·3 per cent.), by Leaf[8] (3 per cent.), and by Delbet (0·84 per cent.).*

Mastitis and malignant growths.—An important difference must be noted between acute and so-called "chronic" mastitis in this connection, owing to the presence of symptoms along with the acute variety, and their relative absence in the chronic variety. Thus in the clinical records of the Hospital mention of chronic mastitis in connection with cancer is only made on three occasions. From histological examination, however, it is clear that the two conditions are frequently met with in conjunction. This point is dealt with later (p. 118).

In the case of acute mastitis the evidence is somewhat more satisfactory. Recent acute mastitis was twice immediately followed by cancer, which developed once in the same breast, once in the opposite breast. Acute mastitis occurring some years previous to the onset of growth, as determined by records subsequent to 1878 (1,020 cases), affected the same breast in 46 cases (4·5 per cent.); both breasts in 6 cases (0·59 per cent.), and the opposite breast in three cases (0·079 per cent.).

De Morgan's spots (telangeiectases)—These are recorded in 15 instances among 907 female patients with carcinoma of the breast between 1886 and 1903, giving a percentage of 1·6. It is noted that in the cases in which the spots were present the disease was generally still in an early stage. In one instance it was stated that they had existed for years.

Œdema.—Local œdema over the shoulder or the thorax is recorded but 6 times. In the majority of these cases the œdema occurred at an advanced period of the disease, persisted for a long time, and showed an extensive distribution. Œdema of the arm is, of course, a much commoner occurrence, being recorded in 169 cases (*i.e.* 10·6 per cent.). In degree it varied within wide limits.

In 3 cases the patient's attention to the breast was first drawn by the appearance of œdema of the arm. These cases

* Cited by Roger Williams, *loc. cit.*

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were examples of growths beginning in or near the axilla. As a rule, œdema of the arm is a late symptom, seldom appearing in the first year after the commencement of growth, and generally during the second or third year. The average length of time between the commencement of the mammary disease and the onset of œdema of the arm has been in The Middlesex Hospital series 4 years and 2 months. It is frequently noted that it occurred in cases that had undergone operation, especially when the operation had been followed by recurrent growth in the axillary part of the scar or in the axillary glands.

(B) Secondary Growths in Cases of Cancer of the Breast.

The question of the distribution, site, etc., of the secondary deposits has been investigated over a series of 1,110 cases of which there are no records of death, and 470 cases, not included in the preceding series, which died in the Hospital. For the first series clinical notes alone are available, for the second series access is possible to both clinical registers and post-mortem registers. Below is given in a tabular form the main distribution of the secondary growths.

TABLE III.

Table showing the Distribution of Secondary Growths in cases of Carcinoma of the Breast.

	Post-mortem Evidence. (470 Cases.)	Clinical Evidence. (1,110 Cases.)
No metastases	15	70
Skin only	0	90
Skin, axillary glands, and sometimes pectoral fascia (no metastases in viscera).	58	465
Metastases in thoracic organs (abdomen free) ...	76	4
Metastases in abdominal organs (thorax free) ...	46	5
Metastases in thoracic and abdominal organs ...	160	1
Distribution, various	112	378
No evidence for or against metastases	3	97

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Amongst the above cases, secondary nodules were found in bones only on 11 occasions; in axillary glands and brain, 4; in abdominal organs and bones, 4; in abdominal organs and brain, 2; in thorax and brain, 5; in thorax, abdomen, and brain, 4; in thorax and bones, 7. In all the cases in which a post-mortem examination revealed the absence of metastases the patients died from intercurrent diseases (pneumonia, erysipelas, etc.) shortly after the operation.

The above table has a diagnostic importance. In cases of short duration the figures placed under "clinical evidence" may be taken as adequate, but the longer the duration of the cancer before it comes under observation the more we must consider the case in the light yielded by the post-mortem evidence. For most of the secondary nodules mentioned in the above table, at a certain period of the disease are present even when clinical examination cannot succeed in detecting them.

In two instances secondary growths were found in the viscera at the autopsy, and yet no axillary glands were present. These patients had been operated upon some time previously with clearing out of the axilla.

A noteworthy point concerns the frequency with which the abdomen alone is affected by secondary growths. Thus out of the 470 cases secondary growth was present in the abdomen alone in 46, in the thorax alone in 76, and in both abdomen and thorax in 160 cases.

Site of secondary growths.—Below is given the distribution of secondary growths, according to the organ or tissue affected. The two groups (clinical and post-mortem) are quite independent series of cases.

TABLE IV.

Table showing in detail the Sites of Secondary Growths in 1,580 cases of Cancer of the Breast.

Organ or Tissue.	Recognised during Life, 1,110 Cases.	Recognised Post-mortem, 470 Cases.
Axillary glands	725	354
" on both sides	30	43
Cervical and submaxillary glands ...	131	127
Bronchial and mediastinal glands ...	5	81
Inguinal glands	9	9
Lumbar "	0	12
Mesenteric "	0	28

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TABLE IV.—*continued.*

Organ or Tissue.	Recognised during Life, 1,110 Cases.	Recognised Post-mortem, 470 Cases.
Subclavicular glands	9	7
Subpectoral lymphatics	14	8
Skin (*a*) ulcerated	321	255
„ (*b*) adherent only	333	87
„ (discrete nodules)	77	81
Thoracic wall	72	135
Pectoral muscle (and fascia)	120	40
Opposite breast	52	85
Parietal pleura	11	160
Lungs (and visceral pleura)	9	163
Axillary vessels	6(α)	6
Thyroid gland	0	9
Larynx	1	0
Heart (mostly auricle)	0	11
Pericardium	0	41
Peritoneum	2	37
Liver...	9	212(β)
Stomach and intestine	1	16(γ)
Kidneys	1	41
Pancreas	0	16
Spleen	0	13
Suprarenal	0	35
Uterus	1	5
Ovary	0	24
Bladder	0	4
Fallopian tubes	0	1
Brain (and Meninges)	4	23
Medulla	1	3
Facial Nerves	1	4
Muscles:		
Sterno-mastoid	0	1
Glutaeus	1	1
Forearm	0	1
Lumbar	1	1
Deltoid	0	2
Abdominal	1	0
Bones:		
Skull	2	16
Facial bones	0	2
Vertebral column	3	32(δ)
Femur	9	28
Humerus	3	15
Scapula...	1	3
Clavicle	2	9
Leg	2	2
Fore-arm	0	1
Sternum	5	1
Pelvis	1	5
Ribs	9	41

(α) Artery 1, vein 5.
(β) Of these, 5 in the gall bladder, 1 in the round ligament.
(γ) 1 in the Ampulla of Vater.
(δ) 7 dorsal, 10 lumbar, 1 cervical: in the remainder the situation was doubtful.

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The percentages yielded by the above figures correspond well with those given by other authors excepting in certain instances, which are as follows:

TABLE V.

Organ or Tissue.	The Middlesex Hospital (Autopsies).	Gross (Autopsies).	Török and Wittelshoefer (Autopsies).
	Per cent.	Per cent.	Per cent.
Skin (discrete nodules)	17	—	10
Pectoral muscle	8·6	—	16
Opposite breast	18	7·8	9
Bronchial and Mediastinal Glands	17	—	6·8
Pleura	34	50·9	—
Lungs	34	49·9	—
Brain	4·9	9·4	—
Bones	33	20·5	—
Ovary	5·1	8·9	—

In no case were secondary growths found in every organ without exception, nevertheless in one case almost all organs of the body were involved, but the liver was free from growth.

Combining the data of the clinical and post-mortem evidence we see that

68 per cent. of all cases had metastases in the axillary glands;

4·6 per cent. showed growth in the axillary glands on both sides;

16 per cent. had metastases in cervical glands.

5 per cent. had metastases in bronchial and mediastinal glands.

63 per cent. the skin was involved, being either ulcerated or adherent.

10 per cent. of the cases showed discrete secondary skin nodules.

It is also interesting to note that the absolute number of secondary growths is greater for the liver (212) than for the lungs (163).

Concerning the femur and humerus, in the greater number of the recorded cases mention is made of fracture; thus the femur is recorded as being the seat of growth 37 times,

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and the seat of fractures 26 times. In the humerus the figures are 19, with 6 fractures. It would probably be unsafe to conclude that the figures given for metastases in bones represent the truth, in view of the relative infrequency with which detailed examination of the skeleton is made at autopsies.

The site of cancerous deposit in the femur is, according to the order of frequency, (*a*) subtrochanteric region, (*b*) the middle of the shaft or boundary between upper and middle third, (*c*) inferior extremity. In 8 cases both femora were involved, and in 3 both humeri.

The cause of death in cancer of the breast.—Taking 459 cases of cancer of the breast in which the cause of death was plainly stated and recognised at the autopsy, in 371 the death was directly due to cancer, in 88 it was due to some non-cancerous condition. These cases are subdivided as follows:—

A. *Death caused by Cancerous Growths.*

1. General dissemination of growth throughout the body accounted for 165 deaths, *i.e.*, about 36 per cent.

2. No special cause found at autopsy in 50 cases, *i.e.*, 11 per cent. These cases showed simply a cancer of the breast and chest wall, but no vital organ was damaged. In 15 of them the growth was large and ulcerated, and yielding much discharge. Many of the patients were emaciated. This class corresponds to cases dying from exhaustion. Many of them show an irregular temperature and suggest the condition of chronic septic absorption.

3. Invasion of several important abdominal organs 49 cases, *i.e.*, 10·6 per cent.

4. Pulmonary and intrathoracic growths alone were fatal in 49 cases, *i.e.*, 10·6 per cent.

5. Secondary deposits in brain were prominent in 19 cases (some of them gave definite symptoms during lifetime, as follows:—Coma 2, giddiness 1, acute insanity 1, paralysis 5).

6. 15 were cases where death was caused by considerable extension of the growth to the pleura and pericardium without any other growth. In two the thorax was opened by the ulceration, and in one the heart itself was laid bare.

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7. A great pleural effusion was the direct factor of death in 11 instances.

8. Paraplegia due to the pressure of spinal nodules and with fatal issue was noted 11 times.

9. Hæmorrhage from the breast through erosion of an artery caused death in two cases.

B. *Non-Cancerous conditions causing Death.*

The non-cancerous conditions causing death were 88 in number, *i.e.*, 19 per cent. They may be divided as follows:—

Pulmonary and Cardiovascular Systems: Pleuro-pneumonia 16, bronchitis 5, pulmonary tuberculosis 2, tuberculosis of pericardium 1, pulmonary gangrene 1, pulmonary embolism 4, pulmonary œdema 4, perforation of axillary vein at operation 1, post-operative thrombosis of axillary vein 2, post-operative thrombosis of vena cava 1, gangrene of leg (thrombosis) 1, fatty degeneration of the heart 4, brown atrophy of the heart 1.

Septic Causes: Erysipelas starting from the ulceration 8, after operation 4, septicæmia (spontaneous) 2, after operation 5, pyæmia (post-operative) 5, acute pericarditis 4, acute peritonitis 4, empyæma 4.

Gastro-intestinal and others: Intestinal obstruction (ulceration of colon with peritonitis due to pressure of uterine fibroid) 1, incarcerated hernia 1, nephritis 1, granular kidneys 2, cerebral softening 1.

(C) Clinical Observations.

In the present section certain clinical details are dealt with statistically as far as is possible. The subject of age is considered separately in another page.*

Civil State.—Taking 1,000 female patients, between the years 1876 and 1903 inclusive, who were suffering from cancer of the breast, and in whose cases there is satisfactory information on this point, we obtain the following figures:—Married with children 673, married without children 99, unmarried 228. Thus, the married constitute 77·2 per cent.

* Lazarus-Barlow, "Cancer-ages" (This volume, p. 26).

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and the unmarried 22·8 per cent., a ratio closely corresponding to the proportion of married and unmarried females above the age of 25 in the general population of London as determined by the last census, and indicating that the liability of married and unmarried women to cancer of the breast is about the same.*

Occupation.—Of the 772 married women and of the 228 unmarried women 699 and 103 respectively were occupied with house-work, the occupations of the remainder were as follows :—

Married with Children.—Dressmakers, tailoresses, 21; cooks, 16; laundresses, charwomen, 12; nurses, 7; schoolmistresses, 5; servants, 5; factory and shopwork, 7.

Unmarried.—Dressmakers and needlewomen, 28; servants, 24; cooks, 22; ladies' maids, 15; nurses, 14; schoolmistresses, 8; laundresses and charwomen, 6; factory and shopwork, 8.

Pregnancy.—Cancer developing in the course of pregnancy is recorded 5 times. Pregnancy taking place in patients suffering from cancer of the breast is also recorded in 5 instances. These cases are different from those just mentioned. Two of these were found at the post-mortem. In another case pregnancy occurred twice while the patient was the subject of a cancer of long duration. In two, operation was done (amputation of the breast) without causing abortion or any other trouble.

Lactation.—In spite of the importance of this consideration, satisfactory details are given in but a small proportion of the cases. In 74 cases full information is found on the subject, of these 43 suckled with both breasts a great number of children; 5 did not suckle at all; 13 did not suckle with the breast which subsequently became the site of cancer, because it gave no milk in consequence of having been the subject of inflammation at some date prior to the pregnancy; 6 suckled only with the breast which was invaded later by malignant disease, the other breast giving no milk owing to

* According to Leaf (*loc. cit.*) and Gross (*loc. cit.*) cancer is about five times as common in married as in unmarried women, but there is no evidence that either author makes correction for the relative numbers of the two classes in the population generally.

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previous inflammation. In 3 instances over-lactation lasting for 18 up to 30 months, is recorded. In 4 others under-lactation was met with, suckling being discontinued after a fortnight or so. In 9 instances cancer of the breast developed during lactation.

Menstruation.—The subject of menstruation considered in a broad sense in its relation to cancer will not be dealt with in the present Paper. The entire subject is sufficiently important to call for a separate treatment and a communication thereon will be made in a future volume of the Reports.

Complexion and colour of the eyes.—In 128 cases a note was given on this point; 112 of these were dark and 16 were fair. The proportion of dark and fair individuals in the London lower classes according to Beddoe (quoted by Roger Williams) is 43 per cent. for the first, and 57 per cent. for the latter. Dealing with patients affected with carcinoma of the breast, Roger Williams himself found that 61 per cent. were dark and 39 per cent. were fair. Our figures, so far as they go, also indicate a greater propensity of dark subjects to develop malignant growth of the breast.

Family history of tuberculosis.—The relation of family history of tuberculosis to the occurrence of cancer generally was discussed by Hillier and Tritsch, and by Pearson in Vol. III. of the Archives of The Middlesex Hospital. With regard to cancer of the breast exclusively, in 1,000 cases, tubercular family history was definitely recorded in 18·6 per cent. of the cases; the respective proportions for the married and unmarried women being practically the same (viz., 18·8 per cent. married, 17·7 per cent. unmarried). Much attention has been paid to this point at The Middlesex Hospital, as shown by the notes, so that we can confidently compare this figure with those of Leaf (39 per cent.) and Roger Williams (55 per cent.).

History of previous injuries.—The previous occurrence of injuries to the mammary glands, such as blows, falls, has been recorded with great care in our Registers, and an injury of some sort is met with in 17·9 per cent. of all cases, the respective figures being 18·7 per cent. for married and 15·1 per cent. for unmarried women. In view of the general excellence

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of our source of information on this point it is remarkable that the figures differ so markedly from the percentages given by Leaf (35 per cent.) and Roger Williams (25·5 per cent.).

Family history of malignant growths.—As in the cases of tuberculosis and of injury, the Records of The Middlesex Hospital are extremely valuable in respect of the family history of Cancer. The subject in general has been treated at length in Vol. III. of the Archives. While other authors have found evidence of this factor in 23 per cent. (Leaf) and 24·2 per cent. (Williams) of the cases, the 1,000 cases of mammary cancer used for the present communication return the proportion as 15·6 per cent. (unmarried 14·2 per cent. and married 16 per cent.). Though markedly lower than the figures given by Leaf and Williams, this value is nearly twice as great as the figure (8·56) given by Hillier and Tritsch (*loc. cit.*, p. 133) for a family history of cancer in patients themselves suffering from cancer (not exclusively mammary).

Homologous heredity (*i.e.* a patient with cancer of the breast giving a history of malignant disease also of the breast in mother, sister, or aunts) was present in 26 of the 1,000 cases. On 16 occasions this homologous heredity obtained in married women and on 10 occasions in unmarried women, a remarkable difference if one bears in mind the fact that the proportion of women in the same 1,000 cases was 773 married to 227 unmarried.

"Cancer à deux."—In the case of only 3 patients was it said that the husbands were affected with cancer (2 of the "throat," 1 of the "tongue").

Consanguinity of parents.—In two instances the parents of cancerous patients were cousins, but in both of these cases the family history was good.

In a certain number of cases two or more of the three factors, family history of malignant disease, family history of tubercle, and a history of personal injury, were combined in the same patient; these are as follows:—

Family history of tubercle with history of malignant growths, 25.

Family history of tubercle with history of personal injury, 29.

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Family history of malignant growths with history of personal injuries, 20.

Family history of tubercle with family history of malignant growth and personal history of injury, 6.

Dealing with the 4 groups of cases just mentioned, the proportion of married and unmarried women affected is as 4 to 1, *i.e.* as their relative numbers in the general population of London.

General health and emaciation.—Information on this point has been derived from 500 otherwise unselected cases of mammary cancer, which were chosen as presenting satisfactory information on the point. The description given is in all cases the condition "on admission," and no notice is taken of the question whether the patients have or have not undergone operation.

Emaciated during the 1st year of the disease	24 (4·8 per cent.)
Emaciated after the 1st year of the disease	208 (41·6 ,,)
"Fairly well nourished" . . .	17 (3·4 ,,)
"Well nourished"	251 (50·2 ,,)

The last class of the "well nourished" may be sub-divided as below, if we take into account the duration of the disease:—

"Well nourished" in the 1st year of disease	151 (300 per cent.)
"Well nourished" in the 2nd year of disease	34 (6·8 ,,)
"Well nourished" in the 3rd year of disease	25 (50 ,,)
"Well nourished" after the 3rd year of disease	43 (8·6 ,,)

Speaking generally, emaciation is a late symptom in carcinoma of the breast, unlike the early starvation cachexia caused by a growth situated in the œsophagus or stomach. Accordingly in our notes we seldom find mention that the appetite has been seriously affected. Out of 1,000 cases, in 7 only did the anorexia take a prominent place among the other symptoms.

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Pain.—Pain in the affected breast is described as shooting, pricking, darting, throbbing, stabbing, etc. However accurately defined, the character of the pain throws little or no light on the nature of the growth.

Of 462 cases with sufficient reference to this point pain was present in 443 (*i.e.* 95·5 per cent.), and absent in 19 (*i.e.* 4·5 per cent.). The absence of pain in the latter cases was not dependent upon the early stage of the disease; on the contrary, all presented appearances of being advanced cases. It may therefore be stated that pain is a nearly constant accompaniment of carcinoma of the breast; though, as will be seen later, it is not the principal, and is seldom the first, sign of the disease.

Effects of pressure.—Apart from the appearance of œdema, considered previously (p. 94), pressure on the axillary nerves may cause definite symptoms. In 8 cases numbness of the arm was a prominent feature of the disease. In 23 patients the muscular power of the arm was diminished, not only by the weight of the œdema, but also by pressure on the brachial plexus leading to partial or even to complete paralysis. In 3 instances the volume of the limb became so considerable and the pain so distressing that amputation was performed as a last resource.

Other conditions.—Other pathological conditions clinically recognised during the stay of the patients (entire series of 1,581 cases) in the Hospital were as follows:—

Actual tuberculosis of the lungs, 15; gastric ulcer, 7; severe dyspnœa (effusion), 35; cough, 26; bronchitis, 15; pneumonia, 3; septic conditions, 7; delirium, 5; acute insanity, 3; coma, 3; optic and bulbar paralysis, 3; convulsions, 6; paraplegia, 8; hemiplegia, 6; facial paralysis, 3. Spontaneous fractures were discovered 13 times. In 2 instances fractures of the neck of the femur occurring *undoubtedly* in cancerous growths are said to have united at least sufficiently well for the patient to be able to get up and walk about with a stick.*

* The question arises whether such cases may be compared with cases of secondary scirrhous cancer of the vertebræ, causing paraplegia and disappearing subsequently (Osler[9]).

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The first sign noticed by the patient.—In order to determine the character of the first sign of carcinoma of the breast an analysis was made of 500 otherwise unselected cases giving information on this point. The first sign noticed by the patient was as follows:—

"A lump" in the breast	315	(63·0 per cent.)
"A lump" in the axilla first	10	(2·0 „)
Growth and pain together	57	(11·4 „)
Pain alone	72	(14·4 „)
Retraction of nipple	19	(3·8 „)
Itching of skin over the breast	8	(1·6 „)
Redness or puckering of skin	5	(1·0 „)
Œdema of the arm	1	(0·2 „)
Ulceration	2	(0·4 „)
Discharge from the nipple	3	(0·6 „)
Bleeding from the nipple	5	(1·0 „)
General weakness	1	(0·2 „)
Paraplegia	1	(0·2 „)
Ascites	1	(0·2 „)

(D) Methods of Operation and their Results.

Of all our 1,581 female patients with carcinoma of the breast, 321, or practically 20 per cent., were inoperable when they first came to the Hospital after a duration of the disease varying from 6 months to several years.

In 40 such cases occurring between the years 1890 and 1903 the total duration of the disease from the appearance of the first sign to the time of the patient's death in the Hospital was 3 years 2 months and a half.* In a small number of these cases in which no operation was performed, spontaneous new formation of epithelium took place over a large ulcer, and the disease continued to extend only in the depth, probably beneath the fascia.

Definite surgical treatment of one kind or another was carried out in 1,260 cases.

(1) **Caustics.**—Use of caustics notably after the method devised by Dr. Fell, which relied chiefly upon the application

* Taking 25 cases of spheroidal cell carcinoma (microscopically determined between 1900 and 1904) the corresponding figure is 43·6 months.

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of chloride of zinc paste in incisions made into the growth, was much in vogue at this Hospital in the fifth decade of last century. Apart from a specific report on Dr. Fell's methods presented by the Surgeons, the notes on this subject are scanty and of an historic interest only.

(2) **Methods of amputation.**—We shall now compare the three principal surgical methods which have been applied to the affection. They are (*a*) partial or complete amputation of the breast; (*b*) amputation of the breast with clearing of the axilla; (*c*) amputation of the breast and clearing of the axilla with removal of pectoral fascia, pectoral muscle, etc.

(A) Partial or Complete Amputation of the Breast alone.—Roughly speaking this operation was usual from 1858 up to 1875. Later it has also at times been performed when the breast was considered to be the sole seat of disease. Of 200 otherwise unselected patients who underwent only this strictly local operation, 109 (54·5 per cent.) returned to this Hospital for local recurrences, the first reappearance of the disease taking place on an average 22 months after the first operation. Death occurred on an average 2 years and 10 months after the operation (Winiwarter, 22 months), and the total duration of life in cases so treated was, on an average, 4 years and 8 months from the time when the disease was first noticed by the patient (Winiwarter, 50 months; Gross, 52 months).

(B) Amputation of the Breast with Clearing of the Axilla.—Roughly speaking this operation was chiefly performed between the years 1875 and 1895, and after that date only when no more extensive removal was needed. Records of 230 patients who were treated by this method are available. Of these 90 (39 per cent.) returned with recurrences, and on an average the first sign of local recurrence was seen 10·5 months after the first operation (Winiwarter, 13 months). The average prolongation of life after the first operation was 29 months. In 45 cases in which the first operation and the subsequent death took place and are recorded in the Hospital the average total duration of the disease was 71 months (Gross, 39·3 months). Subtracting from this figure the value for the duration of life in cases undergoing no operation

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(38·5 months, as given above) it appears that by this operation life is prolonged on an average by two years eight and a half months.

(C) Amputation of the Breast with Removal of Axillary Glands and Tissue, Pectoral Fascia and Muscle, if necessary.—This operation has been performed in this Hospital on 275 patients, chiefly from the year 1894 till the present time. Thirty-eight of these patients (13·8 per cent.) have returned for local recurrences which took place on an average 9·9 months after the first operation.

Of these 275 cases 14 also died in the Hospital. Of this number 7 died within 2 months of the operation, as the result of some condition directly or indirectly arising therefrom. The remaining 7 died at periods varying between 2 months and 4 years after the operation, giving an average duration of life after the operation of 26·1 months.

It is necessary in considering these figures to remember that one has by now obtained a complete list of all patients dying as the result immediate or indirect of the operation. We are thus definitely enabled to state that on these figures the mortality immediately due to the operation is only 1·5 per cent.*

On the other hand one has only obtained a small proportion—and that the least satisfactory—of the cases that recovered well from the operation. Some of these may have already died at other hospitals; but considering the large number of cases on which the operation was performed, and the small number concerning which we know the subsequent duration of life, it is probable that many are still alive, and by their increasing longevity will materially raise the figure for the *true* duration of life after this method of operation. That this assumption is reasonable is further supported by the diminished percentage of recurrences, although here also it must be allowed that we have not as yet received the full tale of recurrences in the 275 cases.

Another point to be remembered is that with the more extensive modern operation, cases that would formerly have been regarded as inoperable, are now dealt with by the

* From 1882 to 1890, according to Roger Williams, the immediate operation mortality at The Middlesex Hospital was 10 per cent.

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surgeon. By their very extensive nature these cases act prejudicially upon the statistics. Hence the cases dealt with by the three classes of operation are not quite comparable since a larger relative proportion of extensive cases of cancer comes into the group now under consideration.

With regard to recurrences themselves under the modern method of operating, it is noteworthy that the percentage of recurrences has steadily diminished. If we adopt the figure for the date of first appearance of recurrence obtained for operation B (10·5 months), it is clear since our 275 cases only deal with operations performed up to the end of 1903, that by the end of 1904 we have already obtained by far the greater proportion of such recurrences as are about to take place. Consequently the figure for percentage of recurrences under the modern operation (13·8 per cent.), though it will be raised, cannot be raised very considerably. Even if we assume that it is doubled, it would show a marked diminution on the earlier figures, that there can be no doubt that the modern method is sensibly diminishing the chance of recurrence.

With regard to the site of recurrences another difference is recognisable. According to old statistics for operations A and B recurrences often took place in the axilla alone. Examination of the 275 cases with reference to this point shows that of the 38 instances in which there was recurrence only 5 took place in the axilla, whereas 26 took place in the scar and neighbouring skin. A partial explanation of this no doubt lies in the great extent of the scar at the present time.

The time of appearance of the local recurrence is about the same (10 months) in operations B and C with clearing of the axilla, as might be expected. But it was longer when the operation consisted in simple removal of the local growth, partly because only far earlier cases were selected for operation, and partly because in the absence of histological examination instances of chronic mastitis were probably included.

NOTE.—Besides the strict mammary operations mentioned above, numerous other methods of treating Cancer of the breast have been tried in The Middlesex Hospital at different times. These have been employed only in inoperable cases,

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and include oöphorectomy performed 6 times (1897 to 1903) alone or in conjunction with administration of thyroiodin,* injection of Coley's fluid, thymic extract,* various sera, etc. None of these calls for further discussion here.

IV.—CARCINOMA OF THE BREAST IN MALES.

Although 26 cases of Carcinoma of the male mamma are recorded at The Middlesex Hospital, notes sufficient for discussion of the points to be dealt with below are only available in 17 of these, 16 being primary, 1 secondary.

Primary carcinoma.—The side affected. In 11 instances the right breast was the site of the growth; in 4 the left; in 1 it was not stated. The great preponderance of cancer of the right breast in males is in marked contrast with the slightly greater tendency of the left gland to be affected in females. These figures corroborate the general result obtained by Roger Williams in 71 cases of cancer of the male breast, collected from literature (right breast 53 per cent., left breast 47 per cent.).

Site.—The site of growth in males is mostly very near the nipple. It was in our cases as follows:—10 times at the nipple, twice central (beneath the nipple), once outside the nipple in the periphery of the gland; and 3 times the point was not plainly recorded. Retraction of the nipple was noted only in one instance.

Ulceration.—Ulceration is the rule in males; of 16 cases, 12 were ulcerated, 4 were not. Owing to the immediate connection between the growth and the skin, ulceration takes place easily, and before retraction of the nipple has time to develop.

Size.—The size of a growth varies in males from a marble to an orange, but is mostly small, and never comparable with the dimensions met with in females.

Œdema of the arm was seen in 3 cases, all of which were of long duration.

* "Oöphorectomy." Pearce Gould, "Brit. Med. Journal," vol. i. 1905. "Injection of Thymic Extract" (Foulerton, "Arch. Middlesex Hosp." vol. ii. p. 144).

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Double primary carcinoma occurred in one case; this was the oldest patient, and he developed carcinoma of the breast at 84 years of age, after he had had carcinoma of the lower lip excised without recurrence 18 years earlier.

Secondary growths.—Fifteen cases showed enlargement of the axillary glands. As the result of 4 post-mortem examinations metastases were found as follows:—Pleura, 1; pericardium, 1; liver, 1; pectoralis major, 3; cervical glands, 1; thoracic wall, 1; skin, 3. According to the same source the causes of death were:—Erosion of the pulmonary artery by caseous bronchial glands (hæmoptysis), 1; thrombosis of the subclavian vein after operation, 1; œdema of the lungs after operation, 1; pyæmia arising from ulcerated breast, 1.

Clinical observations.—*Age.*—Our youngest patient was 38 years, the oldest 84 years old when attacked by carcinoma of the breast. The mean age of the onset of the disease is 52 years (according to Roger Williams 50 years).

Occupation.—The occupations of the patients were as follows:—Instrument maker, clock-maker, engraver, piano maker, painter, shoemaker, joiner, journalist, warehouseman, traveller, shorthand writer, stock keeper, labourer. In 4 instances the occupation was not stated.

Family History.—A family history of tuberculosis was found only once. A family history of malignant growth also only once (according to Roger Williams 24 per cent.). A personal history of injury was recorded 4 times (Roger Williams 53 per cent.).

First Symptom.—The first symptom noticed by the patient was generally a "lump"; in one instance it was secretion from the nipple, in another itching.

Pain.—Pain was recorded as present in only 4 cases, as absent in 5, and is not mentioned in 7. The whole process is therefore far less liable to be attended by pain in males than in females.

General Health.—Of our total, 9 patients were found to be well nourished when they came to the Hospital, several of them after the disease had been in existence over a year. 4 patients were emaciated; in all of these the disease had lasted more than a year and six months.

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Duration.—Up to the time at which the patients came to the Hospital, the disease had lasted on an average 15 months. The total duration of the disease in cases without operation cannot be stated as no such case is recorded in the Hospital Registers. In three instances in which operations were performed and the patients died in the Hospital, the duration of the disease was 5 years, 4½ years, and 2 years respectively. In two cases death occurred shortly after the operation, but these are not included.

Operations were performed in 12 cases.

1. Four men were inoperable, or refused surgical aid.
2. Two patients were treated with caustics; one of them came back after 3 months with a recurrence.
3. Simple excision of the growth alone was performed on 3 patients. All returned one year or more after the operation with secondary growths in the axilla.
4. In 5 patients the breast and the axillary glands were removed at the same time. In one only the growth is recorded to have reappeared.
5. Two patients had extensive excisions of fasciæ and muscles, but could not be followed later.

Secondary carcinoma of the male breast.—One instance of this extraordinary condition is recorded. In the year 1869 a patient, aged 49, was admitted showing nodules in the axillary gland secondary to an extensive growth of the skin covering the arm. The patient died in the Hospital and at the autopsy nodules were found in the breast as well as in the skin, the pleura, lungs, and liver.

V.—SARCOMA OF THE BREAST.

Forty-five cases of sarcoma of the breast are recorded in the registers of The Middlesex Hospital; 43 are primary (42 females, 1 male) and 2 are secondary (both in females).

FEMALES.—The side affected was left, 23 instances; right 19. Amongst these 42 primary cases the opposite breast was 4 times the site of secondary sarcoma (the right breast once, the left 3 times), so that here, like in carcinoma, the left breast

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seems a little more liable both to primary and to secondary growths.

Site of primary growth.—This was stated in 26 of our cases, and was as follows in two different sets of patients:—

Superior and outer quadrant	5
Superior and inner ,,	3
Inferior and outer ,,	2
Inferior and inner ,,	0
Central	3
Total	13

Superior quadrant	5
Inner ,,	5
Outer ,,	2
Inferior ,,	1
Central	0
Total	13

The above figures show that sarcoma may begin in all points of the breast with a decidedly less frequency at the nipple and in the inferior and inner quadrant, but the numbers are too small to give any percentage worth comparing with carcinoma. As to the site of secondary sarcoma of the breast it was noted in two cases. In one (sarcoma of the chest wall) it was in the upper part of the mammary gland. In the other instance (sarcoma of the right breast) it was in the upper and inner quadrant of the left breast. Though the nipple itself was never the first site of sarcoma, retraction of the nipple took place in 8 instances (19 per cent.).

Size.—On admission the cases of sarcoma of the breast were, roughly speaking, of the following sizes: "hen's egg" or "turnip," 11 cases; "child's head," "cocoa-nut," "man's head," 14 cases. In 17 cases no mention is made of the size. Like patients affected with carcinoma the subjects of sarcoma frequently do not seek surgical advice till a year or more after they have first noticed the growth.

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Clinical varieties.—The name sarcoma is first used in 1865, and very soon after that the spindle cell and the round cell varieties were clearly differentiated. We have sarcoma (no other denomination), 13; cystic sarcoma, 12; spindle cell sarcoma, 9; oat cell sarcoma, 1; round cell sarcoma, 3; and alveolar sarcoma, 1; angeiosarcoma, 1; lymphosarcoma, 1; adenosarcoma, 1. Total 42.

Sarcoma mostly begins with multiple nodules; in one patient 11 different bosses could be counted while the disease was still in an early stage.

Œdema of the arm.—This symptom developed in 4 patients, and always very late.

Gangrene of the arm, through pressure on the axillary vessels, occurred in one instance.

Secondary growths.—Secondary growths in sarcoma of the breast, according to the clinical and post-mortem evidence taken separately, are as follows :—

Clinical evidence (34 cases).—Other breast, right 1, left 3; axillary glands, 25 (one case on both sides); skin, 19; cervical glands, 6 (one on both sides); thoracic wall, 5; pectoral muscle, 6; pleura, 1. No glands were felt in 9 cases.

Post-mortem evidence (8 cases).—Mediastinal or bronchial glands, 4; axillary glands, 7; pleura, 3; liver, 4; kidneys, 3; pericardium, 1; stomach and intestine, 1; mesentery, 1; brain, 2; sternum, 1; lungs, 1; suprarenal, 1.

Clinical observations.—*Age.*—The youngest patient with sarcoma of the breast was 23 years old at the beginning of the disease, the oldest was 73. The average age at onset (41 cases) was 45·5 years (Roger Williams, 44·8 years).

Civil state.—Twenty-six patients (61·9 per cent.) were married and had children; 13 (30·9 per cent.) were single. The civil state is not given in 3 cases (7·2 per cent.). These figures seem to suggest that the proportion of sarcoma amongst women does not, like carcinoma, correspond to that of the married and unmarried in the population. On the contrary the ratio between unmarried and married women for sarcoma (as 1 to 2) shows that single women are especially liable to be affected by this type of growth.

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Occupation.—Of the married women 24 were engaged in house-work; 2 were laundresses. Of the unmarried 8 did some house-work, 2 were servants, 1 was a teacher, 1 a nurse, and 1 a dressmaker.

Complexion and colour of eyes.—This is stated in only 6 cases; 4 patients were dark, 2 were fair.

Lactation.—Unfortunately no information whatever has been supplied by our notes on this point.

History.—A family history of tuberculosis was present in 7 instances (16 per cent.); a family history of malignant growth in 4 cases (9 per cent.). A history of personal injury was given in 7 cases (16 per cent.). A history of acute mastitis was given in 3 cases (7 per cent.). Lastly, 2 of the patients had contracted syphilis before they were affected with sarcoma.

Pain.—In 25 cases pain was recorded, in 2 it is definitely stated that pain was absent, in 15 instances no record was obtained.

Itching was once the chief and a very early symptom. Ulceration developed in 13 cases (31 per cent.). In 3 of these cases severe bleeding occurred.

Emaciation.—Six patients were emaciated on admission; 12 were described as "healthy-looking." For both groups the average duration of disease before admission had been 17 months (emaciated group 15½ months; healthy-looking group 18½ months).

Duration of Life.—The average total duration of life in sarcoma of the breast as given by 8 autopsies is 26 months (Roger Williams, 31·4 months). This figure is, however, not reliable. That the total duration of life in sarcoma of the breast must be longer than 26 months is shown if duration of life is calculated not from those who died, but from all the 41 cases recorded by the clinical notes. Under these circumstances the average duration of the disease from the first symptom to the time of discharge from the Hospital was 38 months. Therefore the total duration of life must of course be longer than that period.

Methods of operation.—Four cases were inoperable on admission. Partial or complete amputation of the breast was

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performed in 15 cases. 7 returned with recurrences at an average time of 6 months after the first operation. Some of the patients subsequently underwent several operations for recurrence. In one instance 7 such subsequent operations were performed. Amputation of the breast with clearing of the axilla is recorded in 12 instances, 5 of which returned with recurrences at the average time of 5·8 months after the first operation. Amputation of the breast with clearing of the axilla and removal of fasciæ and muscles is recorded in 11 cases, only one of which returned here for recurrence 3 months after the operation.

Secondary sarcoma of the breast.—Apart from the few instances recorded above of metastases or direct extension of growth from one breast to the other, the only two cases where the primary growth was elsewhere were one of melanotic sarcoma of the skin, and one of recurring sarcoma of the chest wall.

Sarcoma of the breast in males.—There is one case only in our Records. The patient was 30 years old; the disease lasted 3 years and the tumour attained the size of a large orange. This was (as often in females) a case of cystic growth.

VI.—THE HISTOLOGY OF MALIGNANT GROWTHS OF THE BREAST IN GENERAL.

In the following paragraphs the histological side of the research is considered. Unfortunately this has not been possible with regard to the entire series of cases which are recorded in the Hospital registers. Hence the number of cases dealt with in the present section is far smaller than that upon which the preceding sections are founded. Nevertheless what they lack in number they gain in accuracy. For every case upon which the present part of the paper is based depends upon carefully revised histological examination. In fact, no single instance—either of a primary or of a secondary growth—has been admitted into the present section without confirmation by the microscope.

It must, however, be acknowledged that in a certain number of cases the diagnoses that have been given would

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probably be open to discussion. This is particularly the case with the group of endotheliomata. There is little doubt that some of the specimens which, after careful consideration, we have admitted to the ever-increasing group of the endotheliomata would be classed by some authors as highly cellular spheroidal cell carcinomata. In the same way there is a certain amount of ambiguity about the term "scirrhus." The extremes of clinical "hardness" and of "softness" are usually convertible into microscopic pictures of varying proportions of stroma and of cells. But a large number of cases is met with histologically which it is difficult to locate.

With regard to the term mastitis one has to distinguish between a form of disease which is very chronic and apparently precedes the onset of the carcinoma and a variety—far more definitely presenting the appearance of an inflammation—which it is probable arises in the tissues subsequent to the onset of the carcinoma, and, indeed, is probably a direct response to the irritation caused by the growth. The latter variety, though definite, is not very common, and for practical purposes the term "mastitis" in the following paragraphs may be taken to mean that which is generally understood by "chronic mastitis."

The cases to be considered here are 300 in number and constitute all the cases of malignant disease of the breast that have been admitted to the hospital between the years 1900–1904 both inclusive. Of this number 28 cases were untreated by operation throughout the entire length of the disease, but died in this Hospital. 33 patients underwent operation at The Middlesex Hospital or elsewhere, and subsequently died here. In 8 cases death occurred in the Hospital, but the question of operation was doubtful, and 231 cases underwent operation and left the Hospital. The total number of autopsies was 69.

Histological varieties of growth.—Of the 300 cases 233 were examples of spheroidal cell carcinoma (95 being described as containing relatively much fibrous tissue and 138 as containing relatively many cells); 12 were columnar cell carcinomata; 23 were sarcomata of different varieties of cell, but mainly mixed, spindle, and round; and 32 were endotheliomata.

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TABLE VI.

Table showing the Numbers and Percentages of the different Histological Varieties of Mammary New Growth (300 cases).

—	Number of Cases.	Percentage.
I. Spheroidal cell carcinoma (mainly fibrous)	95	31·6
I. Spheroidal cell carcinoma (mainly cellular)	138	46·0
II. Columnar cell carcinoma	12	4·0
III. Sarcomata	23	7·7
IV. Endotheliomata (lymphatic type)	31	10·3
Do. (hæmal type) ...	1	0·3

Spheroidal cell carcinoma.—Grouping the varieties together irrespective of whether there was a predominating fibrous or a predominating cellular structure revealed by the microscope, it appears that 78 per cent. of all mammary malignant tumours are built up of spheroidal cells. The average age for this group is slightly over 51 years at the time at which the histological examination was made; in other words, practically, at the date of operation. In 57 cases death occurred in the Hospital, and the average duration of the disease in 54 of these in which the necessary information was available was 49·7 months.

Separating off from the entire group those which show microscopically a great amount of fibrous tissue a remarkable point is disclosed. For whereas the usual belief is that "scirrhous," assuming thereby cases with much fibrous tissue, are of longer duration than highly cellular growths, the records of 24 cases of this type yield an average duration of 44 months, while 30 cases in which the relative amount of fibrous tissue was much less, and the amount of cells much greater, gave an average duration of 54·3 months. Further reference will be made to this point later.

Columnar cell carcinoma.—The proportion of malignant growths with columnar cells (the so-called "duct" carcinoma) in the mammary glands is 4 per cent., and is fairly constant, the actual figures being 2 or 3 cases every year. The average age of the patients suffering from this special growth was 50·6 years at the time of the histological examination. The

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duration of the sole case of this form of disease which is available is 60 months. This corresponds to the opinion held generally that this variety of carcinoma is not quite so malignant as the previous ones.

Sarcoma of the breast.—The above table indicates for sarcoma of the breast a ratio of 7·7 per cent., the actual total number of cases being 23. These may be subdivided as follows: mixed cell 9; round cell 10; spindle cell 3; uncertain 1. At the time of microscopical examination the average age of the patients with sarcoma was 51·0 years, that is to say, very nearly the same as for carcinoma. The total duration of the disease (when controlled by post-mortem and histological examination) was 56·5 months (six cases).

Endothelioma of the breast.—Only one example of hæmal endothelioma was recorded (0·3 per cent.). The remaining 31 cases, representing 10·3 of all malignant growths of the breast considered in this section, were of the lymphatic type. The average total duration of the disease in these cases was 72·2 months, but this figure is derived from 4 post-mortem records only. Reference has already been made as to the possible divergence of opinion of histologists with regard to the cases that we have included in this group.

Chronic mastitis.—This condition was met with in 64 instances, *i.e.*, in 21·3 per cent. of the malignant growths of the breast considered in this section. It is interesting to compare the relative occurrence of this histological change in the different varieties of malignant tumours:—

Character of Growth.	Mastitis Present.
Spheroidal cell carcinoma (mainly cellular)	25·4 per cent.
Spheroidal cell carcinoma (mainly fibrous)	24·2 ,, ,,
Columnar	8·3 ,, ,,
Sarcoma	0 ,, ,,
Endothelioma	15·6 ,, ,,

The preponderance of mastitis in cases of carcinoma is very definite, and there is but little difference according to the

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relatively fibrous or relatively cellular character of the growth. In the case of sarcoma, the absence of evidence of mastitis in the microscopic sections may signify the real absence of mastitis in conjunction with sarcoma; but it is equally possible that evidences of a pre-existing mastitis may have been destroyed by the rapid growth of a fundamentally cellular mass.

Average age.—Comparing the average ages of the patients suffering from malignant mammary growths whose diagnosis was ascertained by histological examination, we find them to be as follows: spheroidal cell carcinoma (mainly cellular) 50·6 years; spheroidal cell carcinoma (mainly fibrous) 50·4; columnar cell carcinoma 50·6; endothelioma 52·1; sarcoma 51; so that they are all comprised within the narrow limits of less than 2 years. Although they are only averages, their persistent coincidence with the first years following the menopause is worthy of remark.

Total duration of the disease.—Taking cases that underwent operation along with those in which no operation was performed, the average total duration of the disease was as follows:—In spheroidal cell carcinomata (cells predominating) 54·3 months; in spheroidal cell carcinoma (fibrous tissue predominating) 44 months; in sarcoma (6 autopsies) 56·5 months; in endothelioma (4 autopsies) 72·2 months. Only one case of columnar cell carcinoma (60 months) is available on this point.

The contrast between the average duration of life in what may be for convenience spoken of as "cellular" and "fibrous" spheroidal cell carcinoma is so remarkable and so contrary to what was expected that a special examination was made of such cases as underwent no operation and died in the Hospital. Fourteen cases of this kind in which the growth was fibrous (*i.e.*, microscopically contained a large amount of fibrous tissue and relatively few cells) gave an average total natural duration of the disease as 25·4 months, with a maximum duration of 48 months and a minimum of 9 months. On the other hand, 11 cases in which the growth was cellular (*i.e.*, microscopically contained a large number of cells and relatively little fibrous tissue) gave an average

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total natural duration of the disease as 65·9 months, with a maximum of 180 months (2 cases) and a minimum of 10 months. Even if we eliminate the two cases of excessive duration we still find that the average total natural duration is 41·7 months. There can, therefore, be no doubt that the fundamentally cellular type of carcinoma lasts longer than the fundamentally fibrous type. It is noteworthy that the average total natural duration of 3 cases of (microscopically determined) endothelioma—equally a cellular growth—is 61·3 months. Similarly, the total duration of (microscopically determined) sarcoma according to The Middlesex Hospital Records—operated cases alone—is 56·5 months. The conclusion to be derived from The Middlesex Hospital Records seems inevitable that the expectation of life is longer with a cellular than with a relatively non-cellular type of mammary growth.*

In seeking an explanation of this unexpected result the incidence of secondary growths in the two types of case is instructive. Autopsies were performed on 32 cases in which the growth was predominantly cellular, and in 25 cases in which it was predominantly fibrous. Speaking generally the secondary growths were widely spread throughout the body in both types, but the "fibrous" type of growth showed a markedly greater tendency to affect important organs. On the other hand, metastases in bones were commoner with the "cellular" carcinomata. This is shown below :—

Site of Secondary Growth.	Fibrous Spheroidal Cell Carcinoma.	Cellular Spheroidal Cell Carcinoma.
Liver	64 per cent.	46·9 per cent.
Lungs	44 „	40·6 „
Kidney	12 „	9·4 „
Brain	8 „	6·2 „
Stomach, intestines, and peritoneum	12 „	6·2 „
Bones	36 „	46·9 „

* The statement made above must not be misconstrued. The usually received clinical teaching that a "hard" or "scirrhous" growth mainly consists of fibrous tissue must however be reconsidered. For, just as a Hunterian chancre may be cartilaginous to the touch, and nevertheless consist principally of cells, so a mammary cancer which is clinically "scirrhus" may show on microscopical examination that cells, and not masses of fibrous tissue, are the predominating feature.

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It would therefore appear probable that the greater tendency of the fibrous type of carcinoma to affect secondarily important organs explains—at least in part—the shorter duration of life in such cases. How far the difference between the duration in the two types of disease as given above depends upon the (generally) smaller size of the hard growths and in consequence upon a less early recognition by the patient, it is impossible to say.

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MALIGNANT DISEASE OF THE LIVER AND BILE PASSAGES: A STATISTICAL STUDY OF THE RECORDS OF THE MIDDLESEX HOSPITAL.

By HECTOR COLWELL, M.B.

In the succeeding pages the liver is considered not only from the point of view of being a primary seat of growth, but also as the seat of metastatic deposits. Indeed, in the case of the liver the latter is in some respects the more important. As an appendix, reference is made to certain other hepatic conditions found in cases of carcinoma where the liver itself is not the seat of growth.

The data for this paper have been obtained fundamentally from the series of post-mortem registers of The Middlesex Hospital from 1854 to the present time. These registers contain accounts of over 12,500 autopsies. Important corroborative evidence has, however, been furnished by the volumes of clinical notes. From the latter source is derived all clinical information such as the occurrence of attacks of biliary colic, and in certain instances the duration of the disease from the onset of the first recorded symptoms.

In the first section primary malignant disease of the liver itself is considered; in the second similar conditions affecting the gall-bladder and bile passages; and in the third, malignant disease of the liver and bile passages which is secondary to new growth in some other organ. In a final section are included observations upon cirrhosis, lardaceous disease and gummata, so far as they appear related to the present subject.

Of the 12,500 cases which were subjected to post-mortem examination, about 3,300 are cases of malignant disease. Of the latter, 41 were cases of primary carcinoma of the liver

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excluding the bile passages, 31 affected the bile passages primarily, and in 608 the liver was affected secondarily. Hence the liver itself was affected primarily in 1·2 per cent. of all malignant disease, the bile passages in 0·9 per cent., and either primarily or secondarily the liver as a whole in 20·6 per cent.

I.—PRIMARY MALIGNANT DISEASE OF THE LIVER EXCLUDING THE GALL-BLADDER AND BILE PASSAGES.

All the cases falling under this heading which are reported in The Middlesex Hospital registers are entered as "carcinoma" or "cancer," excepting three cases which occurred recently and presented the histological features of endothelioma. It may be mentioned in this connection that systematic histological examination of all cases in which there was any suspicion of malignant disease has been conducted in these laboratories since 1900. Primary carcinoma of the liver itself is seen under one of four types, none of which is defined by any very sharp boundary. Hence in some cases there is difficulty in deciding the group to which a given case belongs. The system of classification which is here adopted is as follows:—

(A) Primary carcinoma of the liver with *one* primary focus.
(B) Primary carcinoma of the liver with *several* primary foci.
(C) Primary carcinoma of the liver with cirrhosis.
(D) Diffuse primary carcinoma of the liver.

(A) Primary carcinoma of the liver with one primary focus.—Cases in which this condition obtains (15 cases) show a large mass of cancer occupying one part of the liver. It may or may not be sharply defined by the surrounding liver tissue, but in any case it may be associated with nodular metastases in the organ itself as well as elsewhere. Cases which should properly be included under group B may simulate this condition when numerous neighbouring nodules have coalesced. Under these circumstances, however, the outlines

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of component nodules are distinguishable, and the correct classification of the case indicated. As will be seen by reference to Table I. the primary mass occupies the right lobe of the liver six times as frequently as the left.

(B) Primary carcinoma of the liver with several primary foci.—In this group of cases (15 instances) there are numerous nodules of new growth scattered more or less discretely through the liver. These nodules vary in size, but never to such an extent that one single nodule may be considered as primary to the exclusion of its fellows. Their consistency is as variable as their size, some being of cartilaginous hardness, others centrally diffluent and superficially umbilicated. The growths indeed resemble those seen in a liver which is the seat of metastatic deposit, and the greatest care is therefore required to exclude any possibility of overlooking a small primary growth, especially in the gastro-intestinal tract, or the neck of the gall-bladder. These growths are moreover frequently surrounded by a hyperæmic zone, and in one case at least there was definite hæmorrhage into one of the larger nodules. Although this is described as being by far the commonest variety of carcinoma of the liver,* being said to occur in over 60 per cent. of all cases of that condition as contrasted with 23 per cent. of those cases which are included under Group A, this is not our experience at The Middlesex Hospital, where the numbers are identical. As will be seen from the Tables included in this paper this form of carcinoma of the liver is much less frequently associated with metastases in other organs than that described in the preceding group.

(C) Primary carcinoma of the liver with cirrhosis.—Of this condition our records contain 10 examples. In only one case were metastases observed in other organs (lung), and in one only were the glands in the hilus stated to be involved. These cases appear to fall into two sub-groups.

a. In the first group there is a large mass of new growth with smaller nodules occurring in a liver which is obviously cirrhotic. These nodules are distinct from the cirrhotic liver tissue which surrounds them, so that a section might be made

* Rolleston, "Diseases of the Liver, Gall-Bladder, and Bile Ducts." London, 1905.

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from such a liver and show macroscopically or microscopically either carcinoma or cirrhosis.

b. On the other hand there are records of two cases in which the malignant disease was of such a character as to require microscopical examination for its discrimination from a simple cirrhosis.

(D) **Diffuse primary carcinoma of the liver.**—Of this condition we have only a single example. The growth was soft, evenly diffused throughout the liver without alteration of its shape, and unaccompanied by cirrhosis. The patient was a woman, aged 61, the liver weighed 123 oz., and no metastases were found. The body was well nourished, and jaundice and ascites were absent.

At the end of the paper are given tables of the cases falling under groups A, B, and C.

Clinical Details in Cases of Primary Carcinoma of the Liver itself.

Sex and age incidence.—Primary carcinoma of the liver excluding the bile passages is much commoner in males than in females. Of the present series of cases 25 occurred in males and 12 in females. The average age of the males was 53·4 years, and of the females 53·1 years.

Gallstones.*—In no case have I been able to discover any evidence of gallstones, either in the reports of the autopsies or in the clinical records, and although 4 cases of intrahepatic gallstones are recorded, in none of them was there evidence of malignant disease either in the liver or elsewhere. This relation between gallstones and primary carcinoma of the liver affords a striking contrast to that holding good between gallstones and the same condition affecting the gall-bladder and main bile ducts.

History of previous diseases.—A history of any condition which could reasonably be considered as an ætiological factor was completely absent from the past histories of all the cases included in the present category. Indeed, with the exceptions that a history of syphilis was obtained in 4 cases,

* The subject of gallstones in relation to carcinoma is dealt with later.

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of gonorrhœa in 2, and of chronic alcoholism in 5, the previous histories of the patients were uniformly good.

Duration of disease.—The duration of these cases from the first recorded symptoms is short. The longest history recorded is under one year, the shortest is one month, and the average duration of the 26 cases in which this point is noted is 4·3 months. These figures have a relatively small value in determining the length of the disease. For the initial symptoms are usually so vague and ill-defined that medical attendance is not sought until the disease has made considerable progress. For how long it has been in existence before the onset of symptoms it is always impossible to say.

Early symptoms.—From the fact that in 80 per cent. of cases of primary massive carcinoma of the liver the main growth is situated in the right lobe, which projects upwards and compresses the diaphragm and base of the right lung, it is intelligible that among the earliest symptoms is frequently pain referred to the lower part of the right side of the chest. This, together with the impaired percussion note from the compressed lung, has sometimes led to an early diagnosis of pleurisy. From the evidence afforded by autopsies it is clear that pleurisy may occur, since it was definitely found post mortem in 4 cases.

Among the very earliest symptoms, however, the clinical records point to vague gastro-intestinal disturbances. Some few patients mentioned alternating constipation and diarrhœa as amongst the earliest signs of their trouble, but the great majority complained of attacks of dyspepsia of a more or less vague type, of which discomfort after food, nausea, flatulence, and vomiting are among the chief features. These again appear in the earliest stages to be amenable to the ordinary methods of treatment applicable to temporary digestive disturbance. Of the 25 cases in which records on this point are available, four expressly state that gastro-intestinal symptoms of all kinds were absent.

Pain.—Although gastro-intestinal trouble seems to be the first symptom which attracts the patient's notice, a sensation of weight and uneasiness in the abdomen is almost always early present. At first vague and ill-defined, these symptoms

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usually soon give way to definite and very considerable pain. Pain appears to be a constant feature in these cases, and in only one case of the 25 in which a history on this point was obtainable was there no history of pain. This case presents other features of interest. The patient (male, age 64) was admitted to the Hospital for gout. He had granular kidneys, subsequently developed uræmia and died. At the autopsy, in addition to the other lesions, the liver was found to be the seat of primary new growth of the nodular variety; the nodules, 12 in number, were somewhat larger than ordinary green peas, and although a primary focus was carefully sought for in other organs, none was found. Under these circumstances it is not surprising that the condition in the liver did not produce any obvious symptoms. This case clearly does not vitiate the statement that pain is a constant feature of primary carcinoma of the liver. The pain in primary hepatic carcinoma appears in some cases to come on or be more noticed at night in the earlier stages, and is then described as of an aching character. In one case, however, the patient appeared to suffer less pain in the recumbent than in the erect posture. Usually these variations soon disappear, and the pain becomes constant usually either in the right hypochondrium (15 cases) or in the epigastrium (6 cases.) It is nearly always subject to marked exacerbations, mostly of a lancinating character, and probably, in part at least, is due to local peritonitis. For a day or so previous to death pain frequently disappears, but this is doubtless due to the condition of the patient and the use of narcotics.

Tenderness over the liver is recorded in 10 cases. It is frequently best marked in the epigastrium (6 cases), and is more obvious when the organ presents nodulation on palpation through the abdominal parietes.

Jaundice.*—Jaundice is by no means an invariable, though a common, symptom. As will be seen from the Tables it was present in 23 of our cases and absent in 18. When present it appears at very variable times in the course of the disease and comes on gradually.

* It must be remembered that slight degrees of jaundice, though easily recognisable during life, are often doubtful or unrecognisable at the autopsy. Hence for the preparation of this section clinical as well as post-mortem records have been consulted

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Ascites.—Ascites is also by no means constant. It was found post mortem in 27 of the 41 cases.

Emaciation.—Emaciation, like the two preceding features, is an inconstant feature. It was found in 28 of the total number of cases, being described as "great" in 12, and "slight" in 16; in 4 cases emaciation was noted as absent, and in 9 cases it was stated that the bodies were "well-nourished" or "fat."

Histology.

Information concerning the histological characters of the growth is possible in ten cases of primary malignant disease of the liver, owing to the preservation of microscopic sections. Below is given a short description of each case.

I. (Table III., No. 7).—The liver presents the histological features of an endothelioma, with certain parts resembling perithelioma. The "lumina" are not invariably round, sometimes being oval, and sometimes irregular. In several instances they are bordered by a fairly well-marked layer of cells, radially arranged. In some places the alveoli are completely filled with cells.

The cells show a large body, a nucleus which does not stain very deeply, and a small amount of chromatin.

The liver itself is the seat of multilobular fibrosis with much small round cell infiltration.

A pulmonary metastasis shows similar arrangement, although the characters of the cells are different.

II. (Table I., No. 12).—Spheroidal cell carcinoma with much fibrosis of the neighbouring liver substance.

III. (Table III., No. 11).—Spheroidal cell carcinoma of an unusual type. Alveoli are present which contain cells of varying size, but mostly small, and oval, irregular, or fusiform in shape. The nuclei of the cells show corresponding variations; for the most part they stain lightly. The alveoli are irregularly arranged throughout the liver substance, and the characters of the cells and their nuclei frequently suggest sarcoma. The liver itself shows degeneration and pigmentation, but no fibrosis.

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IV. (Table II., No. 15).—Columnar cell carcinoma with papillary growths into the alveoli. The cells and their nuclei are elongated and stain deeply.

V. (Table III., No. 8).—Spheroidal cell carcinoma with much young fibrous tissue throughout the liver.

VI. (Table I., No. 12).—Columnar cell carcinoma. Alveoli and cells small, nuclei fairly large, round or oval. Great fibrosis of the liver.

VII. (Table III., No. 9).—Spheroidal cell carcinoma with much fibrosis of liver.

VIII. (Table I., No. 15).—Spheroidal cell carcinoma with much fibrosis of liver. Metastases in intestine, capsule of an ovarian cyst and peritoneum show similar appearances.

IX. (Table III., No. 10).—Endothelioma resembling chiefly the hæmal type excepting that the spaces do not contain blood, and that they are for the most part surrounded by a single layer of cells. Fibrous tissue traverses the entire growth, and it is impossible to say whether the liver was originally cirrhotic or not.

X. (Table I., No. 14).—The nature of the growth is very obscure. In the liver the appearances are indeterminate, but from secondary growths in a cœliac gland and in the biceps muscle it is probable that the growth is in reality endotheliomatous.

II.—PRIMARY MALIGNANT DISEASE OF THE GALL-BLADDER AND BILE PASSAGES.

The Middlesex Hospital Records contain 31 examples of these conditions, 12 occurring in males and 19 in females. As regards its sex-incidence malignant disease of the bile passages is therefore seen to be in striking contrast to primary malignant disease of the liver itself. Clinically, however, both conditions so closely resemble one another that their discrimination is often only made at an exploratory laparotomy or an autopsy. A curious feature of carcinoma of the bile passages, considering that in it gallstones are nearly always found, is the usually complete absence of any history of biliary colic. In the cases considered in the present section, biliary colic was only recorded in 3 instances, in each of which the colic was

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associated with jaundice. The first recorded attack of biliary colic occurred in each case about one year before admission to Hospital.

As regards the precise situation of primary growth, our records contain accounts of cancer at three different situations: (*a*) fundus of the gall-bladder, (*b*) cystic or common duct, and (*c*) ampulla of Vater.

Cancer of the fundus of the gall-bladder is by far the commonest form recorded, and was found in 19 cases (61·3 per cent.). One case was interesting because the new growth occurred in an "hour-glass" gall-bladder. The distal extremity, which was shut off from the main cavity of the viscus and packed with small gallstones, was the seat of the primary growth. Cancers of the cystic and common bile ducts are grouped together, as it is frequently impossible to indicate precisely which was the seat of the primary affection. Cancer in these situations was observed in 11 cases (35·5 per cent.). Of cancer in the ampulla of Vater only one example is recorded. The patient was a man aged 36, emaciation and jaundice were present and no gallstones were found. This case occurred in the year 1869, and the clinical history is defective, but the character of the case is practically certain from the description of the autopsy. Secondary growths were present in the liver.

Earliest symptoms.—Pain.—The earliest symptom in 26 of the 31 cases consisted of dull pain in the right hypochondrium. This pain was fairly constant, but appeared to increase steadily in severity. Almost along with the first onset of pain 8 of the present series showed various digestive troubles, usually commencing with attacks of "indigestion." Vomiting more or less frequent is noted in 25 cases, in 5 no special note on the point exists, and in one gastro-intestinal symptoms including vomiting are specifically stated to have been absent.

Wasting is a far more prominent feature of primary malignant disease of the bile passages than of primary malignant disease of the liver itself; it was found in 93·5 per cent. of our present series, and in 42 per cent. was noted as "marked," "great," or "extreme." In two cases wasting

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was the first symptom noticed, but pain and digestive troubles soon supervened.

Jaundice occurred in 22 of the 31 cases, and is usually a late symptom; but in 5 cases it was reported to have been present for 6 months.

Ascites is noted as present in 13 cases; it is a late symptom appearing a few weeks before death.

The duration of the symptoms accompanying malignant disease of the bile passages in 27 cases upon which notes are available varied from 12 months to one month, the average being 5 months.

Cancer of the fundus of the gall-bladder was associated with jaundice in 10 instances, in 9, jaundice was absent. But in all the cases of cancer in the common bile or cystic ducts, and in the instance in which the ampulla of Vater was involved, jaundice was recorded.

Definite adhesions to surrounding organs are uncommon; in 3 cases, however, the transverse colon was invaded, and in 2 of these the lumen of the bowel communicated with the cavity of the diseased viscus.

Metastases occurring in other tissues than the portal glands and liver are very infrequent, being recorded in only 3 cases (9·7 per cent.). The liver itself, however, is generally the seat of new growth (24 cases or 77·4 per cent.), and one of the deposits is usually a direct extension from the neoplasm in the gall-bladder. In 5 cases (16·1 per cent.) no hepatic metastases were present, although direct extension from the primary growth had occurred. In 2 instances (6·5 per cent.) the sole seat of growth other than the primary was found in the portal glands. In all cases where these glands are specifically mentioned in accounts of post-mortem examinations of cases of malignant disease of the gall-bladder and bile passages, they are stated to be involved. In 3 cases (9·7 per cent.) the peritoneum was affected to a considerable degree, and in one instance (3·2 per cent.) metastatic deposits were discovered in the pleuræ. In no case was a visceral distribution found similar to that which occurs frequently in cases of carcinoma of the breast, rectum, etc. These metastases and extension growths are frequently of large size, and the largest recorded metastasis (not extension) in the liver

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was mentioned in connection with carcinoma of the cystic duct. It occupied the right lobe of the liver, and was said to be about "the size of a fœtal head."

Gall-stones and biliary colic.—It has already been said that a history of previous attacks of biliary colic is in most cases conspicuous by its absence. Our records only contain 3 instances in which biliary colic is said to have occurred; in 2 instances the notes are defective in this respect, but it is fairly certain that there was no biliary colic in the remaining 26 cases. This observation is in complete accord with those of Rolleston and Kehr on the point (*loc. cit.* p. 630). Nevertheless, gall-stones have been discovered at the post-mortem examination in 27 of the 31 cases of primary malignant disease of the gall-bladder and bile passages at The Middlesex Hospital. In the remaining 4 cases of this series it is specifically stated that no gall-stones were discovered. No mention, however, is made on the point of pigmentary débris.

Age.—The earliest age in which malignant disease of the bile passages was observed in a female was 31. The greatest age recorded in a female is 73; the average age for females is 54·76 years. In males the corresponding figures are 36 years and 65 years, with an average age of 51·58. The average age for both sexes is 53·45 years. The fact that the average age of women in cancer of the bile passages is higher than that of men is remarkable and contrary to what obtains for the two sexes in the case of cancer at most other sites.

Histology.

The histology of growths of the bile passages is available in 5 cases of which the microscopic slides are preserved in the laboratories. The appearances are as follows:—

I. (Table V., No. 27).—Columnar cell carcinoma, with much fibrosis.

II. (Table V., No. 28).—Transitional cell carcinoma. The growth closely resembles certain varieties of carcinoma found in the urinary bladder. It shows the presence of irregularly shaped alveoli, some of which are only lined, some partially

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filled, and some completely filled with cells of irregular shape, with irregular, but mostly spindle-shaped, nuclei. The stroma of the growth is highly fibrous.

III. (Table V., No. 29).—Columnar cell carcinoma. The growth is papilliferous; the cells are short, and the nuclei small, and in the main, oval. A fair amount of fibrous tissue is present.

IV. (Table V., No. 30).—Spheroidal cell carcinoma, the alveoli being large and bounded by delicate fibrous tissue, and the cells polyhedral.

V. (Table V., No. 31).—Columnar cell carcinoma, with relatively little carcinomatous tissue and much dense fibrous tissue.

III.—SECONDARY MALIGNANT DISEASE OF THE LIVER.

The materials for the present section of this paper have been obtained from our post-mortem registers from 1854 to the end of 1899. Since the latter date tables showing the occurrence of metastases consequent on new growth in some other situation have been published in reports from the Cancer Research Laboratories.

A Table is appended showing the situation of the primary growth and the relative frequency of hepatic metastases in both sexes. Only those cases have been enumerated in which the precise locality of the primary growth was indicated; such cases as were described under the headings of "glands of neck," "inguinal glands," etc., have been omitted. It will be noticed that however frequently the liver is affected secondarily, it is more common for the organ to show an absence of metastases. The only instances in which the tendency for the liver to be involved is actually greater than for it to be free are primary malignant disease of the pancreas and of the kidney. A remarkable feature of the table is the relatively few cases of uterine cancer which show metastatic growth in the liver. Of other cases, carcinoma of the breast is individually responsible for by far the largest number (35·4 per cent.) of all metastases in the liver.

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Cases of secondary affection of the liver in which only a single metastasis is present are stated to be rare; below is given a summary of those cases which I have found mentioned in the records. The majority of the solitary metastatic nodules are situated upon the surface of the organ, as from the nature of the case a small nodule is less likely to escape observation in that situation than when a series of sections are required for its demonstration. The number of cases in which this condition was noted is 65, the respective primary seats with their frequency being as follows:—Breast, 21; uterus, 13; stomach, 8; face and mouth, 7; rectum 5; œsophagus, 4; vulva and vagina, 2; skin, 2; small intestine, 1; bladder, 1: kidney, 1.

The co-existence of secondary carcinoma of the liver and cirrhosis is extremely rare. Only two cases were found in The Middlesex Hospital records. The first was one of malignant disease of the orbit (male, aged 69), in which there was a solitary metastasis in a cirrhotic liver; the second was a case of malignant disease of the left breast (female, aged 58), in which there were two secondary nodules in a liver similarly affected.

APPENDIX.—OTHER MORBID CONDITIONS OF THE LIVER IN CASES OF CARCINOMA.

Leaving entirely upon one side conditions in which the liver is the seat of either primary or secondary carcinoma, certain morbid conditions of the organ are found with more or less frequency in association with carcinoma elsewhere. In many of these the association is no doubt accidental, and hence detailed consideration is not necessary.

Cirrhosis.—The co-existence of a cirrhotic liver (without metastatic deposits) and malignant disease in some other organ is also rare, and as such cases are interesting from the point of view of the supposed connection between alcohol and cancer a résumé of them is given. Of all the autopsies on cases of malignant disease, 2,634 in number, performed between 1854 and 1900, in only 27 was cirrhosis of the liver found. The situation of the primary lesion, together with

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the number of times each was found in association with hepatic cirrhosis, is as follows:—In females, breast, 6 cases; uterus, 6; colon, 1; in males, mouth and face, 6 cases; stomach, 3; orbit, 1; testis, 1; penis, 1; kidney, 1; inguinal glands, 1.

Lardaceous disease.—The post-mortem registers from 1854 to 1900 contain records of 34 cases of lardaceous disease of the liver, exclusive of those cases which were due to chronic suppuration apart from malignant disease. Of these 34 cases 17 occurred in connection with malignant disease of some organ. Of these latter 3 showed lardaceous disease co-existing with hepatic metastases. They were as follows:—Cancer of the uterus, 1; of the bladder (female), 1; of the duodenum (male), 1. The remaining cases, 14 in number, were distributed as follows:—In females, uterus, 9 cases; breast, 1; ilium, 1. In males, rectum, 1; face, 1; skin of thigh, 1.

Gummata.—Amongst the post-mortem records from 1854 to 1900 (approximately 11,300) the presence of gummata in the liver is noted on 40 occasions. Of these 26 were in males, 14 in females. Of the 40 cases 4 were at the same time the subjects of malignant disease. In no instance were gummata and cancerous metastases present together in the liver. The primary sites of the cancer were in females, uterus, 2 cases; in males, rectum, 1; pancreas, 1.

TABLES.

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TABLE I.—Synopsis of 15 Cases of Carcinoma of the Liver with One Primary Focus.

Collected from the Post-mortem Records of The Middlesex Hospital.

Initials. Register No. Sex. Age.	Jaundice.	Emaciation.	Ascites.	Pain	Remarks upon Primary Growth.	Secondary Growths.
1. E.J. 138/69. F. æt. 41	0	Body fat	0 Some œdema of legs.	No notes.	Large ulcerating mass in right lobe, pushing up right lung.	(1) Several, both lobes of liver. (2) Both lungs. (3) Retroperitoneal glands. (4) Peritoneum.
2. J.M. 93/70. M. æt. 52	+	Slight ...	43 oz. fluid in abdominal cavity.	No notes.	Mass size of large apple, in lobus Spigelii.	(1) Several large masses throughout liver. (2) Both lungs.
3. S.M. 100/74. F. æt. 65	0	Great ...	Small quantity of fluid in abdominal cavity.	No notes.	Large mass in inner half of right lobe.	(1) Nodules in both lobes of liver. (2) Both lungs.
4. G.P. 238/75. M. æt. 58	+	Extreme	0 Œdema of legs	Present	Large mass occupying a quarter of right lobe.	(1) Nodules in both lobes of liver. (2) Glands in portal fissure.
5. J.B. 291/83. M. æt. 62	0	Great ...	A little fluid in abdominal cavity.	Present	Large mass of cartilaginous consistency occupying anterior half of right lobe.	Nodules throughout the liver.
6. E.D. 206/86. F. æt. 53	+	Body fat	53 oz. fluid in abdominal cavity.	Present	Large mass, in anterior part of right lobe, near ligamentum teres.	Nodules throughout the liver.
7. C.P. 103/91. M. æt. 55	+	Slight ...	0 Œdema of legs.	Present	Large mass in right lobe; left lobe free from growth.	(1) Nodules in right lobe of liver. (2) Portal glands.
8. J.G. 243/96. M. æt. 42	0	Body fat	130 oz. of fluid in abdominal cavity.	Present	Large mass centrally softened in left lobe.	Nodules throughout liver.
9. J.M. 137/97. M. æt. 62	+	Body fat	0	Present	Large mass in right lobe	Nodules throughout liver.
10. M.N. 296/97. F. æt. 58	0	Slight ...	15 oz. of fluid in abdominal cavity.	Present	Large mass near suspensory ligament, chiefly affecting left lobe.	(1) Nodules throughout liver. (2) Right pleura.
11. W.S. 76/98. M. æt. 43	+	Slight ...	60 oz. of fluid in abdominal cavity.	Present	Large mass in right lobe	Nodules throughout liver.
12. H.M. 182/01. M. æt. 58	+	Body very fat.	44 oz. of fluid in abdominal cavity.	Present	Large mass in right lobe, soft centrally	(1) Nodules in right lobe of liver. (2) Both lungs. (3) Retroperitoneal glands.
13. J.Q. 69/03. M. æt. 67	0	Slight ...	0	Present	Large mass in right lobe	(1) Nodules in liver. (2) Portal gland. (3) Right suprarenal.
14. W.R. 1/05. M. æt. 42	0	Great ...	Few oz. fluid ...	Present	Large mass in right lobe	(1) Nodules throughout liver. (2) Retroperitoneal glands. (3) Biceps muscle.
15. H.W. 180/04. F. æt. 60	0	Slight ...	120 oz. of fluid in abdominal cavity.	Present	Large mass in right lobe	(1) Nodules throughout liver. (2) Peritoneum. (3) Wall of ovarian cyst.

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TABLE II.—Synopsis of 15 Cases of Primary Carcinoma of the Liver, with several Primary Foci.

Collected from the Post-mortem Records of The Middlesex Hospital.

Initials. Register No. Sex. Age.	Jaundice.	Emaciation.	Ascites.	Pain.	Remarks upon Primary Growths.	Secondary Growths.
1. E.W. 158/54. F. æt. 49	0	Extreme.	A little fluid in abd. cavity.	No notes.	Masses throughout the liver, some the size of an orange.	—
2. L.H. 641/57. F. æt. 48	0	Slight.	Œdema of legs.	Present.	Masses throughout the liver, largest soft centrally.	—
3. R.P. 992/59. F. æt. 60	+	Slight.	Much fluid in abd. cavity.	Present.	Masses throughout the liver, largest soft centrally.	—
4. J.H. 1390/62. M. æt. 46	+	None.	3 pints of fluid in abd. cavity, œdema of legs.	No notes.	Masses throughout, varying in size from a pea to an orange, many softening.	—
5. L.S. 101/73. F. æt. 55	0	Great.	8 pints of fluid in abd. cavity.	No notes.	Nodules throughout, varying from the size of a pea upwards; the larger apparently caused by coalescence of smaller ones.	—
6. J.R. 138/80. M. æt. 62	+	Slight.	0	Present.	Nodules of varying size throughout liver.	(1) Right lung and pleura. (2) Abdominal glands.
7. W.E. 201/81. M. æt. 42	+	Slight.	14 pints of fluid in abd. cavity.	No notes.	Nodules throughout; in the centre of the liver they had coalesced to form hard tracts.	—
8. J.W. 74/84. M. æt. 48	0	Slight.	8 pints of fluid in abd. cavity.	Present.	Large masses throughout, some centrally softened, the largest along anterior edge of right lobe.	—
9. T.C. 164/85. M. æt. 64	0	Body very fat.	0	Absent.	Twelve discrete nodules, somewhat larger than peas.	—
10. E.S. 157/88. F. æt. 38	+	Slight.	2 pints of fluid in abd. cavity.	Present.	Masses throughout the liver, largest the size of oranges.	(1) Nodules in right lung.
11. J.A. 157/90. M. æt. 36	+	None.	Slight œdema of legs.	Present.	Masses throughout the liver, many very soft.	(1) Portal glands.
12. F.C. 276/90. M. æt. 58	+	Great.	0	Present.	Masses in left lobe, largest the size of a tangerine.	(1) Portal glands.
13 H.S. 68/92. M. æt. 33	+	None.	135 oz. of fluid in abd. cavity.	Present.	Nodules throughout; coalesced in places, especially in right lobe.	—
14. J.G. 221/92. M. æt. 55	+	Slight.	20 oz. of fluid in abd. cavity.	Present.	Large nodules throughout the liver.	—
15. W.G. 46/02. M. æt. 62	+	Slight.	0	Present.	Large masses in both lobes.	—

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TABLE III.—Synopsis of 10 Cases of Primary Carcinoma of the Liver with Cirrhosis.

Collected from the Post-mortem Records of The Middlesex Hospital.

Initials. Register No. Sex. Age.	Jaundice.	Emaciation	Ascites.	Pain.	Remarks upon Primary Growths.	Secondary Growths.
1. P.S. 1326/61. M. æt. 50	+	Slight.	5-6 quarts of fluid in abd. cavity.	No notes.	Left lobe almost entirely cirrhotic, large mass in right.	(1) Nodules in both lobes of liver.
2. H.A. 163/72. M. æt. 60	+	Body fat.	6½ pints of fluid in abd. cavity.	No notes.	Right lobe, masses of new growth in cirrhotic tissue. Left lobe typical "hobnail."	(1) Nodules in right lobe of liver.
3. M.B. 274/76. F. æt. 50	0	Great.	Several pints of fluid in abd. cavity.	Present.	Large mass in right lobe, rest of tissue "hobnail."	(1) Nodules in both lobes of liver. (2) Portal glands.
4. G.P. 204/85. M. æt. 63	+	Great.	3 pints of fluid in abd. cavity.	Present.	Large mass in left lobe. Right, advanced cirrhosis.	(1) Nodules throughout the liver.
5. H.G.H. 31/91. M. æt. 65	+	Extreme.	10 pints of fluid in abd. cavity.	Present.	Large nodule in right lobe, none in left.	—
6. A.B. 173/92. M. æt. 50	0	None.	Paracentesis abdominis performed before death.	Present.	Large mass in right lobe.	(1) Nodules throughout the liver.
7. C.H. 9/00. M. æt. 40	0	Marked.	None.	Present.	Large mass in right lobe.	(1) Nodules throughout the liver. (2) Both lungs.
8. G.P. 218/02. M. æt. 48	0	Marked.	Present, but no note of quantity.	Present.	Large mass in right lobe.	(1) Masses in right lobe of liver.
9. C.C. 177/04. M. æt. 64	+	Slight.	50 oz. of fluid in abd. cavity.	Present.	Diffuse infiltration of cirrhotic liver.	—
10. T.S. 270/04. M. æt. 61	+	Body fat.	None.	Present.	Diffuse infiltration of cirrhotic liver.	—
Case of Diffuse Infiltrating Primary Cancer without Cirrhosis.						
11. L.P. 257/01. F. æt. 61	0	Well nourished.	None.	Present.	Diffuse infiltration without cirrhosis.	—

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TABLE IV.—Primary Carcinoma of the Gall-bladder and Bile Passages.

Register Number, Sex, Age.	Jaundice.	Emaciation.	Ascites.	Pain.	Situation of Primary Growth.	Secondary Growths.
1. 572/56. F. æt. 48 ...	+	Present.	0	Present.	Fundus of gall bladder	Nodules throughout the liver.
2. 1272/61. F., æt. 49 ...	0	Marked.	1 pint fluid.	"	" "	" " "
3. 141/69. M., æt. 36 ...	+	Present.	0	No notes.	Ampulla of Vater	" " "
4. 58/79. F., æt. 67 ...	+	Great.	0	Present.	Common bile duct	" " "
5. 236/79. F., æt. 56 ...	0	"	0	"	Fundus of gall bladder	Extension into liver.
6. 35/80. F., æt. 60 ...	+	Marked.	0	"	" "	Nodules throughout the liver.
7. 59/80. F., æt. 50 ...	+	"	Present.	"	Common bile duct	Portal glands.
8. 185/83. F., æt. 61 ...	+	Extreme.	0	"	" "	(1) Nodules throughout the liver. (2) Pleuræ. (3) Peritoneum.
9. 68/84. F., æt. 43 ...	0	Marked.	0	"	Fundus of gall bladder	Nodules throughout the liver.
10. 196/84. F., æt. 42 ...	+	Extreme.	0	"	" "	Extension into liver.
11. 132/85. M., æt. 65 ...	0	Great.	0	"	" "	Nodules throughout the liver.
12. 23/89. F., æt. 61 ...	+	Extreme.	80 oz. fluid.	"	Cystic or common duct ...	" " "
13. 101/90. F., æt. 61 ...	0	Marked.	80 oz. "	"	Fundus of gall bladder	" " "
14. 174/90. M., æt. 45 ...	0	Extreme.	40 oz. "	"	" "	" " "
15. 181/90. F., æt. 73 ...	+	"	60 oz. "	"	" "	Extension into liver.
16. 212/90. F., æt. 31 ...	+	Well nourished.	92 oz. "	"	" "	Nodules throughout the liver.
17. 276/90. M., æt. 58 ...	+	Present.	Small quantity of fluid.	No notes.	Cystic or common duct ...	" " "
18. 175/92. M., æt. 63 ..	+	"	0	"	Cystic duct	(1) Nodules throughout the liver. (2) Peritoneum.
19. 286/92. F., æt. 56 ...	+	"	Small excess of fluid.	Present.	Fundus of gall bladder	Extension into liver.
20. 247/95. M., æt. 51 ...	+	"	52 oz. fluid.	"	Cystic or common duct ...	Nodules throughout the liver.
21. 18/96. F., æt. 65 ...	0	Well nourished.	72 oz. "	"	Fundus of gall bladder	" " "
22. 115/96. M., æt. 36 ...	+	Present.	0	"	" "	" " "
23. 120/96. M., æt. 48 ...	+	"	0	"	" "	Portal glands.
24. 44/97. M., æt. 43 ...	+	"	0	"	" "	Nodules throughout the liver.
25. 147/97. F., æt. 53 ...	+	"	0	"	Common duct	Extension into liver.
26. 123/99. F., æt. 56 ...	0	"	0	"	Fundus of gall bladder	Nodules throughout the liver.
27. 128/99. M., æt. 57 ...	0	"	200 oz. "	"	" "	" " "
28. 98/01. M., æt. 54 ...	+	"	Small amount of fluid.	"	" "	" " "
29. 90/00. F., æt. 58 ...	+	"	0	"	Cystic duct	" " "
30. 254/03. M., æt. 63 ...	+	"	0	"	" "	" " "
31. 211/04. F., æt. 50 ...	+	"	0	"	" "	(1) Nodules in liver. (2) Peritoneum.

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TABLE V.

TABLE SHOWING THE OCCURRENCE OF SECONDARY MALIGNANT DISEASE IN THE LIVER, ARRANGED ACCORDING TO THE SITE OF THE PRIMARY GROWTH.

From the Post-mortem Records of The Middlesex Hospital, 1854-1900.

Site of Primary Growth.	Females.		Males.		Total both Sexes.	
	No Hepatic Metastases.	Hepatic Metastases present.	No Hepatic Metastases.	Hepatic Metastases present.	No Hepatic Metastases.	Hepatic Metastases present.
1. Face, mouth, lip, jaw, &c.	28	2	134	8	162	10
2. Tongue ...	18	2	153	8	173	10
3. Pharynx and larynx ...	8	1	25	3	33	4
4. Œsophagus ...	15	5	48	23	63	28
5. Stomach ...	50	22	65	52	115	74
6. Small intestine ...	5	0	5	5	10	5
7. Colon ...	28	8	21	9	49	17
8. Rectum and anus ...	48	32	53	37	101	69
9. Pancreas ...	4	7	6	14	10	21
10. Peritoneum ...	6	1	8	1	14	2
11. Mediastinum and lungs ...	9	2	18	4	27	6
12. Penis ...	—	—	26	1	26	1
13. Scrotum ...	—	—	4	0	4	0
14. Prostate ...	—	—	4	3	4	3
15. Bladder ...	18	2	12	1	30	3
16. Urethra ...	1	0	1	0	2	0
17. Vulva ...	34	2	—	—	34	2
18. Vagina ...	16	3	—	—	16	3
19. Uterus ...	721	97	—	—	721	97
20. Fallopian tube	1	—	—	—	1	0
21. Ovary ...	40	13	—	—	40	13
22. Kidney ...	4	7	9	7	13	14
23. Testis ...	—	—	4	2	4	2
24. Orbit ...	0	2	3	2	3	4
25. Thyroid ...	2	0	2	0	4	0
26. Skin	6	2	16	3	22	5
27. Breast ...	243	215	2	0	245	215
Totals	1,305	425	619	183	1,926	608

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THE RELATION OF CARCINOMA TO GALLSTONES.

By HECTOR COLWELL, M.B.

WHILE examining the post-mortem registers of The Middlesex Hospital, to obtain material for the paper on malignant disease of the liver in the present volume, all cases of gallstones recorded therein from 1854 to 1899 were noted. Subsequently the records from 1900-4 inclusive were examined with reference to this point. The information so obtained forms the basis of the present short communication, but the two periods are kept separate because of the different values of the records themselves in each.

I.—THE PERIOD 1854-1899.

The total number of autopsies recorded within that period is approximately 11,200. Gallstones are recorded in 359 cases (3 per cent.). Of these 359 cases 120 occurred in males (33 per cent.), and 239 in females (67 per cent.).* Considering the 120 cases occurring in males, 84 (73 per cent.) were found in individuals showing no malignant disease, and 36 (30 per cent.) in those in which malignant disease was present. In females, of the 239 cases 130 (54·4 per cent.) occurred in cases without any malignant disease, and 109 (45·6 per cent.) in cases which were the subjects of malignant disease. The numbers of instances in which gallstones were found, either

* In point of fact, since a greater number of autopsies have been performed on males than on females, gallstones are *more* than twice as common in women as in men.

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with co-existing malignant disease or not, are displayed in the following table :—

Number of Gallstones.	Males.		Females.	
	Malignant Disease absent.	Malignant Disease present.	Malignant Disease absent.	Malignant Disease present.
Single	19	10	22	23
Two or three ...	10	1	18	12
Multiple ...	55	25	90	74
Totals ...	84	36	130	109

From a paper in vol. iii. of these reports* it will be seen that of patients above 35 years of age 2,080 males out of a total of 6,507 (31·9 per cent.) were the subjects of cancer; and of 6,554 females 4,126 (62·9 per cent.) were similarly affected. In other words, in the same number of cases cancer was found in approximately twice as many females as males. Since in the selection of these figures care was taken as far as possible to exclude cases of sarcoma, the same must be done in cases in which gallstones were present. Five cases of sarcoma occurred in each sex in this group, reducing the numbers to 104 females and 31 males suffering from cancer and gallstones. Adopting these figures, 25·8 per cent. of the male cases in which gallstones were found were the subjects of co-existing cancer, and 43·5 per cent. of the female cases. Hence the ratio of male to female cancer (1 : 2) is approximately the same as the ratio borne by gallstone + cancer in males to gallstone + cancer in females. Nevertheless there is a slightly greater liability of males to be the subjects of cancer and gallstones than is indicated by the incidence of cancer in the two sexes.

The next point for consideration is the situation of the primary growth in both sexes where there is co-existing cholelithiasis. For this purpose the alimentary tract has been divided into two broad groups, the first comprising all situations between the lips and the lower end of the

* Statistics of carcinoma, based on the records of the Middlesex and the St. George's Hospitals, by W. S. Lazarus-Barlow and W. Gordon Taylor (p. 136).

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œsophagus, and the second all situations between the cardiac end of the stomach and the anus. The reason for this subdivision was that it was considered probable that conditions influencing the liver would be more likely to affect parts included in the latter group. The figures obtained are shown in the following table. The cases in which sarcomata were found (5 in males and 5 in females) have been omitted, as they were too few in number to serve as a basis for generalizations :—

Site of Primary Growth.	Females.	Males.
1. Breast	34 (32·7 per cent.)	—
2. Uterus	29 (27·9 per cent.)	—
3. Gall bladder	19 (18·3 per cent.)	8 (25·8 per cent.)
4. Lip to œsophagus	2 (1·9 per cent.)	10 (32·3 per cent.)
5. Stomach to anus, with peritoneum and pancreas.	12 (11·5 per cent.)	10 (32·3 per cent.)
6. Other sites	8 (7·7 per cent.)	3 (9·7 per cent.)
Totals	104	31

The association of gallstones with carcinoma of the liver and bile passages is considered in the present volume (p. 130), and will not be further dealt with here.

In order to determine the relative frequency of an association between gallstones and cancer in a particular region, the relative frequency of cancer in the regions named in the preceding table have to be compared with the general cancer incidence irrespective of the presence of gallstones. The materials for this comparison have been obtained from the paper on "cancer ages" in this volume (p. 29). Dealing with 4,504 cases of female and 1,712 cases of male cancer, the natural incidence in various sites is as below :—

Site of Primary Growth.	Females.	Males.
1. Breast	1,760 (39 per cent.)	—
2. Uterus, etc.	2,099 (46·6 per cent.)	—
3. Lips to œsophagus	151 (3·3 per cent.)	1,114 (65 per cent.)
4. Stomach to anus	424 (9·4 per cent.)	537 (31·4 per cent.)
5. Liver, etc.	70 (1·5 per cent.)	61 (3·6 per cent.)
Totals	4,504	1,712

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From the two preceding tables it will be seen that the percentages of cases with co-existing gallstones and cancer agree in the main with the general cancer incidence. Thus, in females, the occurrence of gallstones along with cancer of the breast, with cancer of regions between the lips and lower end of the œsophagus, and with cancer of the alimentary tract, is practically the same as the general incidence of cancer in these parts. Similarly in males the occurrence of gallstones along with cancer of the alimentary tract from stomach to anus corresponds closely with the general incidence of cancer in these parts. Two discrepancies, however, show themselves, viz., cancer of the uterus, and cancer of the tract between lip and stomach in males. Consideration of these anomalies is reserved for the present.

II.—THE PERIOD 1900–1904 INCLUSIVE.

During this period 1886 autopsies were performed of which 987 were in men and 899 were in women. Of the 987 male cases 288 (41 per cent. of all carcinoma cases) were carcinomatous; and of the 899 female cases 411 (59 per cent. of all carcinoma cases) were carcinomatous.

Amongst the 1886 autopsies of all kinds gallstones were found in 102. These were divided as follows:—

Number of Gallstones.	Males.		Females.	
	Carcinoma. (288 Cases.)	Non-Carcinoma. (699 Cases.)	Carcinoma. (411 Cases.)	Non-Carcinoma. (488 Cases.)
Single	7	5	14	3
Two or three ...	0	0	6	1
Multiple	9	9	29	19
Totals ...	16	14	49	23

Thus, in males gallstones were found along with carcinoma in 1 case in every 18; in the absence of carcinoma, in 1 case in every 50. In females gallstones were found along with carcinoma in 1 case in every 8·4 cases; in the absence of

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carcinoma, in 1 in every 21. Hence in males gallstones are met with 2·8 times as frequently in carcinoma as in non-carcinoma cases, and in females 2·5 times as frequently. Here again it is seen that there is a slightly greater liability for males to suffer from coincident gallstones and carcinoma than females.

Now, since of the 1,886 autopsies 987 were in men and 899 in women the percentage of male carcinoma in total male cases is 29·2, and the percentage of female carcinoma in total female cases is 45·7.

Hence the true ratio of male carcinoma to female carcinoma in the five years under discussion is 29·2 : 45·7, approximately 1 : 1·5. But of all cases in which gallstones occurred in males 53·3 were cases of carcinoma, and of all cases in which gallstones occurred in females 68·1 were carcinomatous. Consequently the ratio for the two sexes is 53·3 : 68·1 or 1 : 1·3, which is approximately the same as the liability of the two sexes to carcinoma in the period under consideration.

Dividing the sites of primary growth, as in the previous part of the paper, it is seen that gallstones occurred in the following numbers in the various sites of growth :—

Site of Primary Growth.	Females.	Males.
1. Breast	13 (26·5 per cent.)	1 (6·25 per cent.)
2. Uterus, etc.	20 (40·8 per cent.)	—
3. Gall bladder	3 (6·1 per cent.)	3 (18·75 per cent.)
4. Lip to œsophagus	1 (2·0 per cent.)	4 (25·0 per cent.)
5. Stomach to anus, with peritoneum and pancreas.	9 (18·4 per cent.)	6 (37·5 per cent.)
6. Other sites	3 (6·1 per cent.)	2 (12·5 per cent.)

Adopting the percentage distribution at various sites of the large number of cases given in the table on p. 144 in preference to one compiled from the far smaller number that are available in the years 1900-1904, the following points may be observed:—In females the order of frequency with which the uterus, breast, lower part of alimentary tract, and upper part of alimentary tract, are affected by carcinoma is the same whether attention is directed to the presence of gallstones exclusively or not. In males, on the contrary, though carcinoma of the upper part of the alimentary tract is

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more than twice as common as carcinoma of the lower part, gallstones are seen half as frequently again when the lower part is the seat of carcinoma.

COMPARISON OF THE FIGURES FROM THE TWO SERIES OF YEARS.

Upon broad lines the two sets of figures afford support to one another. Thus there is no doubt that the general tendency is for the frequency with which gallstones are met with in association with cancer at any particular site to vary directly with the frequency with which cancer at that site normally occurs. That this is so is further rendered probable by the fact that in the more recent series of cases the uterus no longer holds an anomalous position in the matter of association of carcinoma with gallstones.

The only anomalous positions now remaining for consideration are the upper and lower parts of the alimentary tract in males. When it is remembered that the total number of cases for the two periods in which cancer and gallstones were associated was only 14 for the upper part of the alimentary tract, and 16 for the lower part, it is clear that no weighty conclusions can be drawn. Nevertheless, bearing in mind the undoubted smaller liability to cancer of that part of the male alimentary tract which lies between the lower end of the œsophagus and the anus, it seems certain that there is a special tendency for cancer in this region to be associated with gallstones, at least in men.

Further the two sets of figures agree in indicating that the liability to the occurrence of gallstones along with cancer in the two sexes practically coincides with the liability of each sex to cancer. At the same time they agree in indicating a slightly greater relative tendency of men to suffer from coincident gallstone and carcinoma.

CONCLUSIONS.

From the preceding facts the following conclusions may be drawn :—

(1) Autopsies performed at The Middlesex Hospital between the years 1854 and 1904 indicate that the occur-

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rence of gallstones in cases of carcinoma in the two sexes is approximately proportional to the liability of males and females to cancer.

(2) Autopsies (at all ages) subsequent to 1900 indicate that gallstones are met with in both sexes approximately two and a half times as frequently in carcinomatous as in non-carcinomatous cases.

(3) The liability of gallstones to be associated with carcinoma is independent of the seat of primary growth. Nevertheless, the lower part of the male alimentary tract appears to be somewhat more closely allied with the presence of gallstones than other primary sites in men.

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MALIGNANT DISEASE OF THE PROSTATE: A STATISTICAL STUDY BASED ON THE RECORDS OF THE MIDDLESEX HOSPITAL.

By J. W. THOMSON WALKER, M.B., F.R.C.S.

I.—INTRODUCTION.

The relative frequency with which cancer of the prostate occurs is stated differently by various authors. Until a comparatively recent date, pathologists and clinicians were unanimous in the opinion that the disease was rare, and according to the older cancer statistics primary cancer of the prostate was very rare. Thus to quote only two statements, striking because of the mass of material with which they deal, Tauchon* found only 5 cases of prostatic cancer in 8298 fatal cases of carcinoma in the death register of Paris. This gave ·6 per mille of the total number or, if only the male subjects were reckoned (1904), the ratio was 2·6 per mille. The figures given by Gurlt † did not differ greatly from those of Tauchon. He examined the records of 10,425 cases of cancer from the three great Vienna Hospitals, and found only 8 cases of cancer of the prostate, a ratio of ·767 per mille or, if only the 2,946 male cases were considered, 2·71 per mille.

More recent statistics give an increased proportion of prostatic cancer. Heinemann ‡ states the ratio at 1·65 per mille in 20,544 cases in the Prussian Hospitals, or 4·18 per mille of male cases.

Although the writers of a later date do not deal with such large numbers of cases, yet the increasing number of undoubted

* Tauchon, Recherches sur le traitement méd. des affect. cancereuses du sein, 1844, quoted Socin u. Burckhardt. Krankh. d. Prostata, 1902.

† Gürlt. Archiv f. klin. Chir., Bd. 25, 1880.

‡ Heinemann. Archiv f. klin. Chir., Bd. 57, S. 911, 1898.

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cases seen by individual observers gives the impression that the actual ratio is greatly in excess of that stated by the older writers.*

The following 16 cases have been collected from the case books and post-mortem records of The Middlesex Hospital. The earliest case is from the records of 1866, and the last died in the Hospital in 1904, a period of 39 years.†

These 16 cases occur in a total of 6,732 cancer cases, which gives a ratio of 2·37 per mille or, if only the male cases (2,073) be taken, a ratio of 7·21 per mille. The total number of cases of cancer is nearly a fifth less than that dealt with by Tauchon, but the number of cases of prostate cancer is much greater and is nearly double that given by the more recently published figures of Heinemann.

II.—PATHOLOGICAL ANATOMY.

1. Site of origin.—There is no precise information in the cases in the records of The Middlesex Hospital, either from the clinical or from the pathological side, as to the site of origin of the growths. Nor is this surprising, for such knowledge can only be gained from examination in the earlier stages of the disease, and these cases were without exception far advanced before they came under observation.

In one case (number 5), it was noted at the autopsy, that "the under surface of the prostate was extensively infiltrated with the growth, and it may possibly have originated here." In another (number 4), the right lobe was stated to be "especially enlarged" on rectal examination. In a third (number 10), the right lobe was "enlarged to the size of a small walnut, and was exquisitely tender." Such information

* Kauffmann bases his description in Socin and Burckhardt's work (Krankh. d. Prostata, 1902) on 22 cases, 13 of which had come under his personal observation. Von Frisch saw 12 cases in 10 years, which were verified by operation or post-mortem examination. (Krankh. d. Prostata, 1899.)

† These cases were all primary tumours of the prostate, and, with one exception, carcinomata. It will be noticed that the number of cases is greater than that used for the preparation of "Cancer Ages" (this volume p. 26). Certain cases which were considered as doubtful when compiling the former paper were re-examined, and are included here.

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does not, however, warrant any conclusion being drawn as to the site of origin of the growth. It is even doubtful, as I shall later point out, whether the last of these cases was certainly malignant.

2. Pre-cancerous conditions.—There is also difficulty in obtaining information in regard to the condition of the prostate previous to the appearance of the malignant growth. Some idea may however be gained by the previous history of the patient, and by the size and appearance of the prostate post-mortem. For it may be ceded that a malignant prostate of the small fibrous type in which the prostate is hardly, if at all, increased in size did not originate in an "adenomatous prostate," and a similar statement may be made where the symptoms of urinary disease were of short duration and a large mass of prostatic carcinoma was found.

Calculus is not likely to be overlooked on the post-mortem table, and its presence or absence assumes a certain importance when one remembers the relation of gallstones to carcinoma of the bile passages. The question of the pre-existence of chronic inflammation of the prostate is one on which it is difficult to obtain definite information. And in the cases here recorded there is no evidence, either clinical or pathological, of previous chronic prostatitis, nor is there any proof by which this condition can be excluded.

a. Senile enlargement.—In 14 of the 16 cases, the duration of symptoms referable to the prostate is noted, in the others no information was given relating to this point. In seven cases (3, 4, 5, 6, 7, 13, 16) the symptoms had lasted one year or less, in one case (12) fourteen months, one case (14) fifteen months, one case (8) sixteen months, one case (10) twenty months, one case (9) two years, one case (11) two years and eight months, and in one case (15) twelve years.

Although it is recognised that "enlargement of the prostate" may exist, and may even attain a considerable size, without giving rise to symptoms sufficiently striking to attract the patient's notice, yet this is by no means the general rule, and the absence of symptoms pointing to enlargement of the prostate may be looked upon as having some value in the

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question whether an enlarged prostate preceded the cancerous growth.

If this be accepted it is to the last degree improbable that the 8 cases in which no prostatic symptoms were present up to within 15 months before death, had previously suffered from so-called hypertrophy of the gland.

In the remaining six it is possible that prostatic "hypertrophy" might have pre-existed. Nevertheless, the value of this supposition is somewhat reduced by the uncertainty which exists in regard to the duration of prostatic carcinoma.* Sixteen months does not appear to be over-long for the duration of carcinoma without previous hypertrophy. One of these cases was, however, carefully examined on the first occasion on which he was in the Hospital by two of the surgeons in consultation, and they concluded that there were no signs of malignancy in the enlarged prostate at that time. Six months before death, it was therefore impossible to distinguish the prostatic enlargement from simple "hypertrophy." This points very strongly to the development of malignant growth in a prostate, the seat of simple enlargement. In the case in which the symptoms had persisted for 12 years, the clinical signs were those of simple enlargement, the prostate was enucleated during life, and there is no note of any unusual difficulty during the operation or appearance of malignancy in the specimen before it was submitted to section and microscopic examination, and the patient left the hospital healed, and in good health. These facts would appear to leave little doubt that the malignant process started in a gland which had already for some years been the seat of simple enlargement.

The occurrence of malignant growth in a "hypertrophied" prostate is a point of some interest from the pathological standpoint, and of undoubted importance to the clinician. Apart from stone formation, which is excessively rare in this connection, it is the only definite "pre-cancerous" condition as yet described. Clinically the gravity of this relation between simple and malignant enlargement of the prostate has

* In 46 cases of carcinoma of the prostate collected by Wolff (Deut. Zeitschr. f. Chir. Bd. 53), the duration of symptoms from the first onset to the time of death was some months to one year in 39·1 per cent., one to two years in 28·2 per cent., two to two and a half years in 8·7 per cent., and three years and over in 24 per cent.

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become accentuated since the operation of prostatectomy has been more widely practised.*

(*b*) *Calculus.*—In one case (number 12), a small black irregular calculus was found in the prostate at the autopsy. In another (number 3), pieces of phosphatic grit were passed, during the course of the disease, from a bladder the seat of chronic cystitis, and "a few small masses of concretion" were found in the bladder post-mortem. The combination of vesical phosphatic calculi with malignant disease of the prostate, † though certainly less often recorded than might be anticipated, can hardly be of great importance in view of the frequent co-existence of cystitis. And when these are eliminated, so small a residue of true prostatic calculi remains that their ætiological relationship to prostatic cancer is very doubtful.

3. Characters of tumour.—Of the 16 cases a post-mortem examination was made in 10, in one the prostate was enucleated and the specimen afterwards found to be malignant, and in one a portion of the prostate was removed for examination after suprapubic cystotomy. In one of the 10 cases in which a post-mortem examination was made there is no note of the size of the prostate, but in each of the remaining 9 cases there was a considerable increase in size of the gland. These were described as "much enlarged, 2 inches in diameter" (1), "a large, firm, fleshy mass projecting into the bladder" (3), "the size of an adult fist" (4), "a large mass spreading widely" (5), "much enlarged in all its lobes" (7), "the size of half an orange" (9), "a large tumour the size of a tangerine orange" (11), "considerably enlarged" (12), and "much enlarged" (16).

In carcinomatous prostates that are fairly circumscribed and do not infiltrate the surrounding tissues extensively the enlargement varies considerably. Kaufmann ‡ gives the

* Of late, attention has been drawn to this subject more particularly by French authorities. Albarran and Hallé (Ann. d. Mal. d. Org. génito-urin. 1898–1900) found 20 specimens which they considered showed signs of malignancy among 100 cases which were stated to have died with simple hypertrophy of the prostate. Pousson found 5 out of 23 specimens removed by prostatectomy in which "the prostatic neoplasm departed more or less from the benign and reverted to a carcinomatous form." (Bull. et mêm. de la Soc. de Chir., Paris, 21. 1904.)

† Spanton ("Lancet," 1882, i. 1033) relates a case in which a phosphatic stone co-existed with a large sarcomatous tumour of the prostate.

‡ Art. in Socin u. Burckhardt. Krankh. d. Prostata, 1902.

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average as between a child's fist and an orange, and states that this in general is less than the bulk of sarcomata of the prostate. This marked enlargement is by no means invariable, however, and, as von Recklinghausen * pointed out, the cancerous prostate may be scarcely enlarged or even smaller than the normal gland. Where the consistence of these prostates was noted it was in most cases firm or hard. In 4 (1, 5, 9, 12) the growth was "firm and fibrous" or "hard," in 2 (2, 7) it was of "stony hardness." In 2 cases the prostate was "fairly firm" (16) and "firm fleshy" (3). On section the tumours presented a thick fibrous stroma with soft whitish nodules or the "appearance of a typical scirrhus"; one prostate (4) had a semi-translucent whitish surface, and another (16) was pinkish white in colour.

4. Anatomical types of growth.—There are two fairly distinct anatomical types of prostatic carcinoma: (*a*) one in which the growth extends widely, and a diffuse mass occupies the whole pelvis, and (*b*) one in which the growth has not extended beyond the coverings of the gland.

(*a*) *Diffuse Carcinoma.*—Guyon described this variety under the name "la carcinose prostato-pelvienne diffuse." † In this the growth passes beyond the limits of the gland and infiltrates the areolar tissue of the pelvis, matting the pelvic organs together in an inseparable mass. This spread to the pelvic areolar tissue was seen in case number 5. In the pelvis in this case there was "a large mass of cancer surrounding the rectum and involving the recto-vesical pouch and spreading widely on both sides." The iliac vessels were also surrounded. In another case (number 2) the growth was less extensive, but "the pelvic peritoneum and origin of the folds of the lateral ligaments of the bladder were infiltrated with cancer," and the rectum was firmly adherent to the back of the bladder through the medium of the growth.

In these two cases the bladder and urethra were free from disease; in one (number 2) the ureters appear to have escaped, but in the other both those ducts were involved and their lumen obstructed, the ureter and renal pelvis in each side being dilated. The rectum was infiltrated with growth and

* Festschr. zu Virchow's Geburtstag. Berlin, 1891.

† Bull. méd. Paris, 1887, i. 1339, 1888, ii. 83, 99.

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its mucous membrane ulcerated in both cases. In both, the pelvic lymphatic glands were enlarged from deposits of growth, and enlarged lymph glands were noted in the lumbar and inguinal regions (number 2), and in the iliac and lumbar regions "as high as the origin of the renal arteries" (number 5). In the latter case there was œdema of the legs, and it was noted that the iliac veins were surrounded by the growth and their lumen narrowed. There was no thrombus blocking the veins. In this case there was no further metastasis of the growth ; in case 5, on the other hand, secondary nodules were disseminated through the liver, and there were several small deposits in each lung.

Forgue * appears to be of opinion that this diffuse prostato-pelvic infiltration is a later stage of the type in which the cancer is confined within the limits of the prostatic coverings, or at least does not extend widely in the areolar tissue of the pelvis, for he describes the latter form as not having had time to extend beyond the limits of the gland. This is not however borne out by clinical and pathological evidence. For there are many cases recorded in which the prostatic cancer was confined within the limits of the prostatic sheath for several years, while, on the other hand, the diffuse prostato-pelvic type may have a comparatively short history. In case 5, the more extensive of the two belonging to this type, the symptoms were first noticed three months before death. In the other case the duration is not definitely stated ; the symptoms of the secondary deposits in the liver completely overshadowed those of the local condition. The two types appear to be anatomically distinct and independent of chronological factors.

(*b*) *Circumscribed carcinoma.*—The remaining cases were of the circumscribed type. In this the general outline of the prostate was maintained, although in all instances changes from the normal shape were produced by outgrowths in one or more directions. Of these, extension into the bladder is the commonest in The Middlesex Hospital series.

5. Directions of spread.—(*a*) *Towards the bladder.*—The relative infrequence with which the bladder is involved in prostatic carcinoma has been the subject of comment by

* Article in Traité de Chir., Duplay et Reclus, vii., 1899.

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Guyon* and others. Kaufmann's† series of 100 collected cases showed a much greater number in which there was an extension to the bladder. He found the bladder affected in 57 cases. The cases here recorded show a still greater proportion, and if it be permissible to estimate the percentage of so small a number of cases the proportion works out at 80 per cent.

Of 10 cases in which a post-mortem examination was obtained the growth had extended to the bladder in 8, (numbers 1, 3, 4, 7, 9, 11, 12, and 16). In 3 of these (numbers 7, 9, and 16), the ureters were involved, and in one (3) the prostatic urethra was surrounded, the "canal being completely invested by it." In these cases the bladder extension was in the form of a large nodular mass (9), or as several small nodules at the bladder base (1, 4, 11). In two of these the mucous membrane was ulcerated, apparently "from the breaking down of these nodules" (1, 4). In other cases the prostatic growth projected into the cavity of the bladder as a large fleshy mass (3), or as a cauliflower-like excrescence (7), or again as a "papillomatous out-growth continuous with a part of the growth in the prostate." In one case (16) "the base was infiltrated by the prostatic growth, and the mucous membrane covering it was shreddy." In two cases (9, 16) the ureters were involved and partly occluded by the mass projecting into the bladder; in another (7) the ureteral orifices at the trigone were patent, but immediately outside the bladder the ducts were surrounded and constricted by the growth. In three cases (4, 7, 12) the prostatic tumour had spread to some extent along the outer surface of the bladder base. This is apparent from the statement in the post-mortem records that the seminal vesicles were partly surrounded or almost buried in the growth. This direction of spread of prostatic carcinoma is one of the few which may be estimated on clinical examination, and is, I believe, even more frequent than these cases indicate.

(*b*) *Towards the rectum.*—The growth had encroached upon the wall of the rectum in two cases (2, 5). And in both of these there was ulceration of the rectal mucous membrane.

* "Leçons cliniques sur les affect. chir. de la vessie et de la prostate," Paris, 1888, and "Leçons cliniques sur les maladies des voies urinaires professées à l'hôpital Neckar." Paris, 1894. † *Loc. cit.*

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In one "the rectum was shrunken, and was firmly bound down to the back of the bladder below the level of the lateral ligaments. There was no complete stricture of the gut, but the narrowing ceased about three inches from the anus, or exactly opposite to the prostate. Here the lining membrane of the anterior wall of the bowel was the seat of a small circular ulcer, the size of a shilling, with raised but cleanly cut margins, and a deep villous base. The coats of the bowel in the neighbourhood of the ulcer were much thickened."

In the second case the growth affected the rectum "three inches above the anus, where it appeared as several prominent nodules. The mucous membrane was destroyed over a small area." Both these cases were of the diffuse prostato-pelvic type.

(*c*) *Towards the pelvic peritoneum.* — The pelvic peritoneum was involved in one case (2), and in this case there were also deposits strewn over the general surface of the parietal peritoneum.

(*d*) *Towards the lymphatic glands.*—Metastatic deposits in the lymphatic glands are mentioned in six of the ten cases in which an autopsy was made. In only three of these (1, 2, 5) was it stated that the lymph glands of the pelvis were the seat of deposit. If in the remaining 7 cases the absence of any mention of enlarged pelvic glands may be taken to mean that these were not affected, the number (3 in 10) corresponds very closely with Kaufmann's estimate of 27 in 100 cases.

The lymph glands ranged along the course of the iliac vessels were enlarged with secondary deposits in two cases, those along the aorta in the lumbar region in 4 cases, the mesenteric glands in one case, and the inguinal in 2 cases. The deposit in the inguinal glands is interesting, as it appears to represent a metastatic spread against the lymph stream. In one case however (12) the following note appears in the post-mortem record:—"The growth in the prostate invades the tissues for a short distance around, upon the left side towards the corpus cavernosum." This affection of the inguinal glands is found apart from any encroachment on the penile tissues in the other case, and it appears in 16 of Kaufmann's 100 cases.

The lymphatic glands are considered later in more detail.

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III. — SECONDARY CHANGES IN THE URINARY SYSTEM RESULTING FROM PROSTATIC CARCINOMA.

Before passing to the consideration of metastases of these tumours, it is convenient to note at this point the secondary effects of the prostatic growth upon the urinary system. These effects consisted either of obstruction or septic inflammation, or a combination of the two. Of the 10 cases in which the kidneys, ureters, and bladder were examined post-mortem, no secondary disease of the bladder or kidneys was noted in two cases. In the remaining 8 cases two showed chronic interstitial nephritis, which was probably unconnected with the prostatic growth. In 6 cases there were changes in the bladder and kidneys, and in one changes in the bladder only, which resulted from the presence of the tumour of the prostate.

There was well-marked obstruction in 6 cases, and in 2 of these septic infection was superadded. In one case there was septic infection of the bladder and kidneys without obstruction.

In the obstructed cases the bladder was "hypertrophied and fasciculated" in 4, in one the state of the bladder muscle is not mentioned, and in another the bladder was stated to be "dilated." In the latter case there was no invasion of the bladder or urethra by the growth, and it is possible that the dilatation may not have involved any change in the walls of the viscus, but was merely a temporary condition. In the remaining 5 cases the growth had projected into the bladder, and in several of these had assumed large proportions.

It is interesting to note that in the single case where sepsis was present without obstruction, the growth surrounded the neck of the bladder and prostatic urethra.

The ureters and pelves of the kidneys were dilated in 5 cases. In three of these the dilatation was bilateral, and in 2 only one side was affected. Of the 3 cases of bilateral dilatation, the obstruction was situated outside the bladder in the pelvic course of the ureter in 2, and in the remaining case a large mass of growth inside the bladder occluded the ureters.

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In one of the cases in which the ureteral obstruction was unilateral the growth had infiltrated the wall of the bladder, and spread on the right side around the orifice of the ureter and occluded it. In the second unilateral case the right ureter was dilated and patent, so that the ureter had probably yielded, owing to obstruction at the outlet of the bladder, and was not directly compromised by the papillomatous growth that occupied the neck of that viscus.

In 6 cases changes were present in the kidneys, which resulted directly or indirectly from the presence of the prostatic tumour. In two there was suppurative pyelonephritis, and in one of these the condition had been super-imposed upon chronic nephritis. In the other case "the left kidney had evidently been involved later than the right, as the dilatation of the ureter was less, and the organ had undergone physiological hypertrophy." In two cases there was a moderate degree of hydronephrosis on one side, and in one of these the remaining kidney showed chronic nephritis. A small pyonephrosis was present on the right side with chronic nephritis of the left kidney in one case, and in the sixth case it is noted that the left kidney was large and hypertrophied, and the right kidney atrophied to some extent.

IV.—METASTATIC GROWTHS.

The spread to lymphatic glands has been mentioned on a previous page. In one out of 10 cases there were no secondary deposits, either in lymph glands or in other organs (9). In this case the prostatic growth was of considerable dimensions, and the bladder was extensively involved. In three cases deposits were present in lymphatic glands, but not elsewhere (5, 7, 16). One of these was of the diffuse prostato-pelvic type; in the other two the growth had projected into the bladder. The lymphatic glands were affected in common with various organs in 4 cases (1, 2, 11, 12). In two cases (3, 4) there were deposits in organs, but no mention was made of the lymph glands.

Next in frequency to the lymph glands metastatic deposits were found in the liver and lungs. Each of these organs was

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affected alone in one case; in two both the liver and the lungs were the seat of deposit.

The pancreas, suprarenal capsule, kidneys, testicle, and peritoneum were each affected once.

The following table shows the relative frequency of metastatic deposits in the various organs :—

METASTATIC DEPOSITS.

Lymphatic glands	7	Lungs	3
Pelvic	3	Pancreas	1
Iliac	2	Suprarenal capsule	1
Lumbar	3	Kidneys	1
Inguinal	3	Testicle	1
Mesenteric	1	Peritoneum	1
Portal	1	Hepatic flexure of colon	1
Liver	3		

The relatively large number of cases in which the lymphatic glands were the seat of secondary deposits in this series, and the fact that the liver and lungs were next in point of frequency, is in accordance with the experience of observers who have dealt with large numbers of collected cases, or have recorded series of personal observations. There is, however, a form of metastasis, striking in its frequency and its intimate relation to prostatic cancer, that finds no place in this series. Von Recklinghausen,* in 1891, pointed out the peculiar tendency of prostatic carcinoma to form metastatic deposits in the bony skeleton, and the special form which these deposits assumed, and he recorded 5 cases upon which he based his description. Before von Recklinghausen's publication a few isolated cases, such as those of Thompson,† Silcock,‡ Förster§, and Julien,‖ had appeared

* Die fibröse und deformirende Ostitis, die Osteomalacie und die osteoplastischen Carcinome in ihren gegenseitigen Beziehungen. Festschrift zu Virchow's 71 Geburtstag. Berlin 1891.

† Trans. Path. Soc. London, 1854. p. 204.

‡ Idem. 1883, 84. xxxv. 244.

§ Würzb. med. Zeitschr. 1861. Bd 2. quoted Socin und Burckhardt "Krankh. d. Prostata," 1902.

‖ "Étude sur le cancer de la prostate." N. dict. de Méd. et Chir, prat. Paris, 1880. xxix. 697. quoted do.

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without special notice having been drawn to their peculiar features.

Von Recklinghausen indicated, as a feature of prostatic carcinoma, the tendency of the bone metastases to plastic formation of bone, and he drew a parallel between this and mammary carcinoma. This tendency was present but less marked in thyroid, gall-bladder, stomach, pancreas, and bronchial carcinoma. The osteoplastic growth, whether occurring as nodules in the interior of the bones, or as a widespread infiltration, was combined in parts with a varying degree of osteoporosis. The osteoplasia was always in excess of the rarefaction. Von Recklinghausen described this form of metastases as occurring in cases where the primary tumour was small and confined within the limits of the organ. There were deposits in the lymph glands, but not in the other organs. The vertebræ were most frequently affected. Kaufmann states the ratio of bony metastasis in his 22 cases as 70 per cent. In 34 cases he found the bones affected in the following order:—Vertebral column, pelvis, femur, ribs, sternum, skull, humerus, tibia, scapula, clavicle, fibula, and bones of the forearm.

In the 10 cases here recorded there is no mention of bony metastasis. It is to be noted, however, that a peculiarity of these metastases in prostatic carcinoma is that, from the osteoplastic nature of the growth, there is no tendency to spontaneous fracture, and no change need be apparent in the form and surface of the affected bones. If this be realized it may be allowed that metastatic deposits might have been present in some of the cases without attracting the attention of the pathologist.

V.—HISTOLOGY.

Owing to the fact that the so-called "senile enlargement," "hypertrophy" or "adenomatous enlargement," shows a combination of round-celled infiltration, with apparent increase, and other changes in the glandular elements, the task of deciding upon the malignant or non-malignant nature of some specimens of enlargement of the prostate is a peculiarly difficult undertaking.

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The form of carcinoma arising in the prostate is, in the majority of cases, of the richly cellular type. Whether the gross specimen may conform to the scirrhous type of carcinoma or not, microscopical examination shows that these cancers present a richly cellular appearance. The majority of carcinomata of the prostate are of the small round or polygonal type of spheroidal celled carcinoma, and they have the peculiarity of infiltrating the stroma in fine rows of cells or in small isolated clumps. The entire tumour may thus, in the gross specimen, appear peculiarly fibrous, while under the microscope it is strikingly rich in cellular elements.* This tendency, moreover, increases the difficulty in distinguishing, on superficial examination, a cancerous from an inflammatory infiltration. And further, this carcinomatous infiltration may, as Kaufmann points out, be carried to so fine a degree that individual cells appear to be separated by fine fibrillæ so as to resemble a round-celled sarcoma. It is further to be noted that even in the common form of prostatic carcinoma, the spheroidal celled carcinoma, certain parts may be found in which there is a more or less clearly defined approach to the formation of a cylindrical celled adenocarcinoma. Again, although cylindrical celled carcinoma is found, not infrequently, to be the general structure of the growth in a specimen, yet in some parts of the same specimen the appearances of a spheroidal celled carcinoma are reproduced. Kaufmann states, indeed, that in his 24 collected cases there was no single example of a pure adenocarcinoma.

It will thus be seen that, apart from the consideration of a diagnosis of malignancy in a given specimen of prostatic growth, there is further a lack of definition in regard to the general type of the assured malignant growths. This can only be referred to the most general plan of growth, at the same time admitting that mixed types are the rule rather than the exception.

In one of the cases of The Middlesex Hospital series (No. 1) there is a careful description of the microscopical characters of the primary and secondary growths. The tumour is a

* This observation, which was made independently, is in accordance with the statements of Campiche and Lazarus-Barlow in regard to mammary growths. (This vol., p. 121 note).

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spheroidal cell carcinoma, and the following is a summary of the description :—The nodules in the prostate consisted of masses of round cells with indistinct granular nuclei without any inter-cellular substance. Together with these were many oval or irregular cells with distinct nuclei. These cells, besides forming distinct aggregations, were infiltrated among the fibres of the surrounding tissues; only here and there was the normal structure of the prostate visible. The nodules in the liver were composed of similar cells which were infiltrated throughout the liver tissue. The nodules in the right lung were composed of similar cells, but presented a much greater number of oval or large nucleated cells.

In another case (No. 3) the growth is stated to be a "lymphoma," without any detailed description.

Besides the preceding case, of which a description only is extant, microscopical sections of the growth are available in five cases (numbers 11, 12, 13, 15, and 16), and the following notes are based upon an examination of these sections made for the purposes of this paper.

Case XI.

A richly cellular tumour in which broad septa pass through the growth. The relation of the stroma to the cellular tissue varies at different points of the same section. In the greater part of this tumour the cellular elements are greatly in excess, and the stroma is reduced to fine strands separating large masses of cellular tissue, but without any tendency to alveolar formation. At other parts the stroma is in excess, and the cellular elements consist merely of rows of a few cells lying in spaces in the stroma. The stroma consists for the most part of long spindle cells with the characteristic nuclei of unstriped muscle. Elsewhere the cells are long wavy spindles, and the nuclei long and pointed. Well-formed blood vessels are present in the stroma and a few capillary blood vessels, but the blood supply is nowhere rich.

Cellular elements.—In a large part of the section the cells are arranged more or less regularly around small rounded empty spaces. Here and there a narrow channel may be seen lined with cells. Dotted throughout the cellular part of

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the section are found small regular rounded spaces with a lining of vertically set cells. These cells more nearly approach cylindrical epithelial cells than those in other parts of the section. Elsewhere the cells are large and vary in shape, being for the most part rounded and oval. The protoplasm has a granular appearance. The nuclei are large, oval, and deeply stained. A few rounded nuclei are found.

Lymph gland metastasis.—The appearances are similar to those described in the primary tumour. The cells are somewhat larger, but have the same arrangement around long or round spaces.

The presence of these spaces in the midst of the cellular part of the tumour renders the histological diagnosis somewhat difficult. The whole picture is not unlike that presented by some specimens of endothelioma. The spaces are sometimes rounded and sometimes long channels, or elsewhere they may be quite irregular. If we except the round spaces with vertically arranged epithelium, to which I have already referred, and which will be discussed later, the cells under high magnification do not line the spaces so closely or with such regularity as one would expect in an endothelioma. These spaces, although their edges are pretty well defined, have frequently a lining of nucleus-free protoplasm, or a nucleus is only observed here and there. The nuclei commence only some way back from the margin of the space, and the cells around often show an unstained protoplasm around the nucleus, as if vacuolation of the cell were taking place. These appearances give one rather the impression of a degenerative change taking place and causing the formation of spaces than of the production of cell-lined spaces according to a general plan of growth. I am, therefore, inclined to the view that these spaces result from changes having taken place within the masses of cells of a spheroidal celled carcinoma. The small round spaces lined by vertically placed cells are different in appearance and in significance. They represent the formation here and there of cylindrical celled structures, and show the tendency of the tumour to the formation of a mixed type of growth.

This view of the histology of the tumour is strengthened by finding in the literature a description of similar changes

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by Paltauf and Bamberger,* and Kaufmann† states that he has often observed such changes, and illustrates the appearances of such a section. It must, however, be allowed that certain authors would regard this tumour as an endothelioma.

Case XII.

The growth is a spheroidal celled carcinoma with rather small cells. A section taken of the bladder base covering the prostate shows that the muscle tissue is extensively infiltrated with cells having large round or oval nuclei. A few small round nuclei are also found. The muscle fibres are separated and in many places quite obscured by these cells. Islands of unaffected muscle tissue lie in the substance of the infiltrated part. In other parts of the section there are lines and seams of infiltration, and in these a blood-vessel is usually found in the central axis surrounded by epithelial cells. This spread is no doubt along the perivascular lymphatics.

Sections of the seminal vesicle show that the outer layer of muscle of this viscus is infiltrated by spheroidal cells lying in lines between the muscle fibres. A portion of the right testicle showed parts in which infiltration had taken place in a similar manner.

Case XIII.

The section shows prostatic gland tubules embedded in a stroma which is infiltrated by the growth. At other parts the infiltration is greater in degree and the gland tubules are partly or wholly destroyed. In other areas there are masses of carcinoma without any trace of gland tissue.

The gland tubules in the least affected part vary in size and shape, and many of them do not differ from the tubules of the normal prostatic gland. Prostatic concretions are present in many of the tubules. In some tubules the gland epithelium is reduced to a single layer of low cubical or even flattened cells. In other parts the gland epithelium has become heaped up into many layers, and in a few has

* Wien. klin. Wochenschr. No. 44, 1899.
† Loc. cit.

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apparently quite filled the lumen of the tubule. In most tubules the lining epithelium is clearly defined from the stroma and the carcinoma cells which infiltrate it, but in a few tubules an outward growth of epithelium appears to be taking place, and at some parts these outgrowths are in direct continuity with masses of cancer cells.

The stroma separating these tubules is greater in extent than in the normal gland and consists of unstriped muscle. Between the layers of the stroma, lying in clefts, are rows of cancer cells in twos and threes or in long lines. These cells are rounded, oval, or polyhedral, and have round dark-staining nuclei.

As this infiltration of the stroma becomes more and more marked the gland tubules are seen to be compressed and distorted, and may be found in various stages of disintegration.

In the large solid masses of carcinoma the cells are small and rounded, and are closely packed. On close examination a mass may be found split up into alveoli by fine capillary blood-vessels passing through it. A similar condition in one of Kaufmann's cases is illustrated by that observer. The tumour is a spheroidal celled carcinoma of the type most common in the prostate.

The heaping up of the epithelium in the acini in this specimen is a condition which has given rise to difficulties in the diagnosis of carcinoma of the prostate. This is especially the case in an enlarged gland where an acinus may be filled with proliferated epithelial cells so as to resemble a large alveolus of a carcinoma.

Kaufmann lays it down that in the case of a dilated simple gland alveolus, with marked epithelial desquamation, the epithelial cells are more loosely set, and their nuclei, as a rule, take the nuclear stains poorly. On the other hand in carcinoma the nuclei are mostly well stained, the cells are very nearly equal in size, and go to form a regular epithelial structure. This is no doubt true so far as the desquamative form of epithelial change is concerned, but in this the difficulty in distinguishing the condition from carcinoma is not as a rule great. There are, however, cases in which the epithelium of the gland acini is heaped up into thick masses, which correspond with Kaufmann's description

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of the malignant change in an acinus. This may be found in otherwise normal or in "enlarged" prostates in which no other reason for suspecting malignancy exists. The oblique section of such acini gives appearances very similar to those of the centrifugal growth of a malignant acinus, and increases the difficulty in histological diagnosis. Such conditions must, I think, be looked upon as benign variations in the cell lining of the acini, unless some further histological change, such as infiltration of the stroma by epithelial cells some distance from an acinus, can also be demonstrated.

The difficulty of diagnosis is greatest in prostates, the seat of senile enlargement, where great variations in the size and appearance of the acini are constantly present.

Case XV.

The tumour consists of richly cellular tissue arranged in well-defined alveoli. The stroma is proportionately small in amount. It runs in branching strands throughout the tumour and breaks it up into alveoli of varying sizes. The stroma consists of fibrous tissue arranged in bundles of wavy fibrils. The alveoli are filled with masses of closely packed cells, the well-defined margins of which give a mosaic appearance. The cells are large, and vary in shape, being rounded, polygonal, oval, or sometimes irregular. The nuclei are large and prominent, and oval or round in shape. The structure is remarkably constant throughout the section. The tumour is of the large spheroidal cell type of carcinoma.

Case XVI.

The tissue consists of gland acini in a dense stroma. The acini are grouped into large masses which are separated by broad strands of fibrous stroma.

The groups of acini are formed by a complicated arrangement of irregular, branching, dilated or narrow, small or large spaces lined with epithelium. These acini differ from those of the normal gland in their grouping, their great numbers, and in the irregularity of their size and shape.

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The stroma consists of unstriped muscle with a large proportion of fibrous tissue. The strands separating the individual acini in a group show marked irregularity in the arrangement of their cells. The epithelium lining these acini is very irregular in distribution. On the whole, the cell layer lining the acini is less pronounced than in the normal gland. Here and there the epithelium is heaped up, but in most parts it forms a somewhat irregular single layer which is wanting altogether at intervals. The epithelial cells are very irregular in size and shape. There is everywhere a tendency for the cells to be set vertically, and in the smaller acini this becomes still more marked, and the cells are clearly columnar in type. Intra-acinous papillary growths are present in the larger acini. At the outlying parts of the gland masses the acini are smaller and more crowded. Here the lumina are smaller, and further out the central space disappears, and the cellular elements are reduced to fine solid cell processes. Lying in the denser parts of the stroma groups and rows of cells are found, sometimes with, but often without, a central lumen.

The greater part of this tumour has the appearance of a columnar cell carcinoma, but at the outlying part of the masses of acini the solid cell processes conform to the appearances of a spheroidal cell carcinoma. It is another example of the mixed type found in the prostate.

In this series there were, therefore, 5 cases of spheroidal cell carcinoma, one case of columnar cell carcinoma, and one case was stated to be a "lymphoma."

VI.—CLINICAL OBSERVATIONS.

1.—General.

The average age of the cases was 60 years and 9 months. The following table gives the ages in decades:

Age.	Number of Cases.
Below 50	3
51—60	3
61—70	8
Over 70	2
	16

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The 3 cases below 50 years were aged 38, 42, and 42, respectively. The tumour in the youngest patient is stated to have been a "lymphoma." In the second case there was no microscopical examination, but the small size and stony hardness point rather to carcinoma than sarcoma. In the third case there was no post-mortem examination, and it is, I think, uncertain whether the disease of the prostate was really malignant in nature. Doubtful cases such as the above, when included in so small a series, explain the large difference of 7 years in the mean age given above and that given in "Cancer Ages" (This volume, p. 36).

Wolff* found 6 cases below 40 years of age in 67 collected cases of prostatic cancer. There is no certainty, however, that all these cases were carcinoma. Half of the 16 cases of The Middlesex Hospital series were aged between 61 and 70 years. Kaufmann found 38 out of 100 cases in this decade.

The occupation of the patients is given in the Table at the end of the paper.

2.—History.

There was a note of the family and personal history in 10 cases. The following are points of interest:—

In regard to hereditary diseases, it is definitely stated in 5 cases that there was no history of cancer in the family, and in 4 of these no phthisis could be traced. There was a tubercular taint in one family history, the father having died of phthisis at the age of 52 and a brother at 32.

The personal history of 10 patients is recorded. For the most part it was uniformly good.

Three patients admitted that they had suffered from venereal diseases. One had a urethral discharge 9 years previously, a second had gonorrhœa when a youth, and the third had contracted gonorrhœa 4 or 5 years before and the discharge had never completely disappeared. About the same time he had noticed a chancre, but no secondary symptoms had supervened. This patient was otherwise a strong, hale man. In 13 cases no notes are made on the subject.

* "Deut. Zeitschr. f. Chir." B. 53.

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3.—Symptoms.

The symptoms noticed by the patient at the commencement of his trouble were referred to organs other than those of the urinary system in two cases. In one case (number 2), the first sign of disease was enlargement of the liver and ascites, and these continued to be prominent features of the complaint till death.

In this case a very large liver studded with secondary deposits was found at the post-mortem examination, and there were nodules of growth throughout the parietal peritoneum. The prostatic growth had spread somewhat widely in the pelvis, but the bladder and urethra were free from disease.

In case number 8, the illness commenced with "a good deal of pain at stool and great difficulty in passing motions." The pain and difficulty gradually increased during 12 months, but there is no mention of urinary symptoms. On rectal examination in this case, the prostatic tumour was a hard firm mass which had infiltrated the rectum, and there was a mass of glandular metastatic growth in the lumbar region. A colotomy became necessary to relieve the obstruction.

Symptoms of urinary obstruction were the most frequent initial signs of disease in the remaining cases. In 6 cases the trouble commenced with difficulty in micturition. In two cases (11, 12) there was difficulty alone, in one (6) difficulty was combined with frequency of micturition, in one (7) with pain, in one (9) with frequency of micturition and pain, and in one (10) with hæmaturia.

In two cases (4, 13) the disease was ushered in by a sudden attack of complete retention of urine. In one case (14) the patient noticed a gradually diminishing size in his stream, in another the first symptoms are stated to have been "trouble with his water." This may be taken to mean difficulty in micturition, as he appears afterwards to have been completely dependent upon his catheter and was quite comfortable, passing it four times daily.

Symptoms of urinary obstruction were thus prominent in 9 out of 14 cases. In 5 of these, the difficulty in micturition commenced alone, and in 4 it was combined with other symptoms (frequency, pain or hæmaturia), but was the most marked sign of disease.

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A post-mortem examination was made in 6 of these cases, and in each of them the tumour had projected into the bladder either as a large mass or as nodules at the bladder neck.

Frequency of micturition was present in the early stages of 4 cases, but in none of these was it unaccompanied by other symptoms. In one case (3) it was the symptom which gave the patient most trouble. It was accompanied by hypogastric pain and turbid urine. The patient had noticed no signs of disease until acute cystitis supervened upon a bout of alcoholic indulgence.

In a second case (6) frequency and difficulty commenced together, and were increased after an attack of complete retention. This patient had been in failing health for 6 months before these symptoms attracted his notice.

In a third case, frequency of micturition was an early symptom in combination with great difficulty and pain. In this case a large mass was found projecting into the bladder at the post-mortem examination.

"Pain and weakness across the loins accompanied by bearing-down pain and constipation," was stated to be the first complaint in one case (5). Pain was combined with frequency and difficulty, as has already been described.

Hæmaturia was the first striking symptom in one case (16). There had been some scalding on micturition for some months before the blood appeared, and the hæmaturia was later combined with diurnal and nocturnal frequency of micturition.

Hæmaturia was an early symptom combined with frequency of micturition and with difficulty in two cases, but was less prominent than the other symptoms.

TABLE SHOWING THE MOST PROMINENT INITIAL SYMPTOMS.

1.—*Symptoms of urinary obstruction* :—

(*a*)	Decreasing volume of stream . .	1
(*b*)	Difficulty in micturition . . .	2
(*c*)	,, with frequent micturition .	1
(*d*)	,, with pain	1
(*e*)	,, with frequency and pain .	1
(*f*)	,, with hæmaturia . . .	1
(*g*)	Sudden complete retention . . .	2
		9

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2.—*Frequency of micturition* :—

(*a*)	With pain and turbid urine . . .	1
(*b*)	„ difficulty (*see* 1, *c*) . . .	1
(*c*)	„ difficulty and pain (*see* 1, *e*) .	1
(*d*)	„ hæmaturia	1
		4

3.—*Hæmaturia* :—

(*a*)	Hæmaturia and scalding . . .	1
(*b*)	With frequent micturition (*see* 2, *d*) .	1
(*c*)	„ difficulty (*see* 1, *f*) . . .	1
		3

4.—*Pain* :—

(*a*)	Across loins	1
(*b*)	With difficulty (*see* 1, *d*) . . .	1
(*c*)	„ frequency and difficulty (*see* 1, *e*)	1
(*d*)	„ frequency and turbid urine (*see* 2, *a*)	1
		4

5.—*Symptoms in other organs* :—

(*a*)	Liver and ascites	1
(*b*)	Rectum	1
		2

Duration and course of symptoms.—The average duration of the symptoms from the date of "commencement" to the time of death in 8 cases was 10¾ months. In three cases the symptoms had lasted 14, 16, and 32 months, respectively, in the others the duration was under a year, and, with the exception of one case in which the symptoms had lasted 9 months, they lasted under 6 months (2, 3, 5, 5 months).

The value of the figures given above is doubtful, chiefly because the early symptoms of cancer of the prostate may well be very slight and obscure.

During the whole course of the disease obstruction to the flow of urine was present in 11 out of 14 cases, and in each of

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these the passage of a catheter became necessary. In 9 of these cases, as has been noted, the difficulty was present from the first, and in two of these the retention of urine was complete from the onset. Five cases were completely dependent upon the catheter for a varying time during disease. In one case the obstruction commenced by the "stopping dead" of the urine during micturition now and again, and finally ended in complete retention. In other cases the difficulty gradually increased until the urine could no longer be passed.

Hæmaturia occurred only after catheterisation in one case (7), and apart from surgical interference in 5 cases (9, 10, 14, 15, 16).

In 3 of these cases the blood was fairly constant (12 months in one), and in two it only appeared at intervals. In case 14 the hæmaturia was very inconstant, the urine being at times quite free from blood and again deeply tinged. The blood was mixed all through the urine in this and in the first two cases.

In case 15 the patient had passed blood and clots for 12 years. At first the attacks were at long intervals, some months or a year or two, but later they became more frequent. The urine was passed clear at first but gradually became red, and was followed at the end by a fair amount of clotted blood.

In none of these cases was the hæmorrhage at any time alarming. It was absent altogether as a symptom of the disease in 10 cases.

Pain was present in varying degree in 7 cases. In one case (3) it started as severe hypogastric pain and was a symptom of an attack of severe cystitis. Later there was burning pain at the end of the penis, then the patient began to have occasional pain across the loins, chiefly on the right side. This steadily increased in severity. Post mortem there was double suppurative pyelonephritis.

In another case there was pain across the loins, which later became severe on the left side and in the lower part of the abdomen. Severe pain in the lower part of the back, pain along the urethra to within half-an-inch of the meatus during micturition, pain in the perinæum just before passing water and pain at the end of the penis at the finish were complained of by different patients.

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Pain was not, however, so common or so striking a feature of these cases as one might expect after reading the literature of the subject.

Frequency of micturition was present in 5 cases and always accompanied by other symptoms. In one case nocturnal frequency was present.

Emaciation was observed in 9 out of 14 cases, and in 4 of these it was very marked. In the remaining cases the patients were "fairly nourished," or " rather obese " in 3 cases that died, and one patient was " healthy-looking " and looked " younger than his age," while the other patient showed no signs of emaciation.

The course of the disease and mode of death varied in individual cases. If the 8 cases in which the progress of the disease was followed to the end of the case be considered, there are two cases (2, 8) in which the symptoms at no time pointed to the original disease. These two cases have already been fully described and need no further discussion. In the remaining 6 cases the progress of the case followed one of three distinct lines.

1. In some cases in which the obstruction had increased to the point of catheterisation the bladder became infected, and an ascending infection of the ureters and kidneys followed. These cases (3, 7, 12) died of acute suppurative pyelonephritis.

2. In another case retention and catheterisation was followed by suppression of urine, and slight chronic nephritis was found post mortem (case 4).

3. In other cases there was gradually increasing emaciation and feebleness and death from asthenia (5, 11.) In one of these there was œdema of the left leg and thigh from pressure of the growth upon the iliac veins.

Diagnosis.

Only a few points in diagnosis which are illustrated in these cases need be considered.

In two cases the symptoms pointed to disease of other organs, and there was nothing to indicate the presence of a prostatic new growth. In one of these the diagnosis "carcinoma hepatis with ascites" was made. In the other

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case there was difficulty and pain on defæcation, but a rectal examination demonstrated the presence of a prostatic growth.

Apart from these cases the symptoms indicated the presence either of prostatic or vesical disease, and the further diagnosis depended mainly upon the examination of the prostate by the finger in the rectum. The condition found is noted in 10 cases. There was marked increase in size in 7 cases, which was described as "very large," "much enlarged," "very much enlarged." The enlarged organ was "hard," "hard and firm," "very firm" in 4 different cases. It was nodular in one case and uniformly smooth in another. No statements are made in regard to the mobility of the organ.

Three cases call for more particular notice:—

Case 10, a labourer of 42 years, with a tubercular taint in his family history (the father and one brother died of phthisis), but with a healthy personal history. This patient gave a history of hæmaturia extending over 1½ years, and on admission the prostate was found enlarged and exquisitely tender. Later, a swelling appeared in the perinæum. Judged by the facts that I have found no case of prostatic cancer extending into the perinæum, and that such a history is well compatible with inflammatory trouble, a diagnosis of malignant disease seems doubtful. The patient died, but no post-mortem examination was made.

Two cases (11, 15) illustrate a difficulty in diagnosis of extreme interest. In these cases there was enlargement of the organ that was looked upon as simple hypertrophy. In one case two surgeons, in consultation, decided that "the disease was not malignant," and in the other case suprapubic prostatectomy was successfully performed. In both those cases microscopical examination showed that the prostate was carcinomatous. There can be little doubt that in these cases the malignant growth commenced in a prostate already the seat of simple enlargement. There is apparently nothing in such cases to show the malignant nature of the tumour until the growth has passed beyond the confines of the already enlarged gland, or unless enlarged lymph glands can be felt.

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In 6 cases of this series there was enlargement of lymph glands which was, or might have been, ascertained during life. The groups of glands most readily observed are those in the inguinal region and the pelvic glands. Both groups were stated to be enlarged in 3 cases. The significance of the inguinal group might easily have been overlooked unless the enlargement were very striking, but those in the pelvis are of undoubted importance in the diagnosis of an enlargement of the prostate of doubtful nature.* In 2 cases the lumbar and iliac glands were enlarged and may have assisted in the diagnosis. The spread of the growth beyond the confines of the prostate is a point of diagnostic importance. In two cases the pelvic areolar tissue was widely infiltrated, and in 3 others the growth had spread along the outer surface of the bladder base.

* See foot-note p. 30. vol. iv., 1905, of these Archives.

[TABLES.

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TABLE OF CASES OF CARCINOMA OF THE PROSTATE RECORDED IN THE REGISTERS OF THE MIDDLESEX HOSPITAL.

No.	Reference.	Date.	Age	Occupation, Personal and Family History.	Duration of Symptoms.	Prominent Symptoms.	Description of Tumour. (Post-mortem.)	Local Spread.	Metastases.	Microscopical Diagnosis.	Notes.
1	P.M.R. 238.	1866	67	—	—	—	Prostate much enlarged, fibrous with whitish nodules.	Bladder, pelvic lymph glands.	Right lung. Liver.	Spheroidal cell carcinoma.	Somewhat emaciated, jaundiced.
2	G.R. 482, 392. P.M.R. 50, Med. Series.	1873	42	Painter. Smallpox, rheumatic fever, lead colic, never gout.	—	Ascites, enlargement of liver, rapid emaciation.	Prostate stony hard, centre yellow, margin white.	Rectum, pelvic peritoneum, lateral ligaments of bladder, pelvic glands.	Lumbar and inguinal lymph glands, lungs, liver, colon, parietal peritoneum.	—	Much emaciated, liver adherent to stomach and colon, chronic nephritis.
3	Index No. 848.	1876	38	Police constable. Gonorrhœa, soft chancre.	5 months	Sudden frequency of micturition, hypogastric pain, turbid urine, followed by retention of urine, lumbar pain chiefly right, catheter life, rigors, vomiting.	Large, firm, fleshy mass	Prostatic urethra surrounded, mass in bladder.	Pancreas, right suprarenal capsule.	Lymphoma.	Emaciated, acute suppurative nephritis, contracted bladder.
4	G.R. 68. P.M.R., vol. iv., No. 14.	1878	70	Messenger.	6 days (?)	Admitted with retention of urine, rapid distressed breathing, and feeble pulse.	Prostate greatly enlarged, right lobe especially, size of adult fist, semi-translucent, whitish on section, tuberous outer surface.	Bladder, rectum partly surrounded, seminal vesicles almost buried.	Liver.	—	Slightly emaciated, granular kidneys, bladder hypertrophied, bronchitis.
5	M.R. 355.	1883	52	Carpenter. No family history of cancer, temperate.	3 months.	Pain and weakness across loins, bearing-down pain and constipation, darting pain in left loin and lower abdomen, hard fixed mass in right iliac fossa, œdema of the legs.	White, firm, and fibrous with soft spots.	Widely diffused in pelvis, rectum surrounded and infiltrated, pelvic and iliac glands.	Retroperitoneal glands as high as renal arteries	—	Fairly nourished, ureters and pelves of kidneys dilated, left kidney hypertrophied, right kidney atrophied, iliac vessels surrounded by growth.

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TABLE OF CASES OF CARCINOMA OF THE PROSTATE—*continued.*

No.	Reference.	Date.	Age	Occupation, Personal and Family History.	Duration of Symptoms.	Prominent Symptoms.	Description of Tumour.	Local Spread.	Metatases.	Microscopical Diagnosis.	Notes.
6	S.R. 1426.	1888	57	Bootmaker. No serious illness, no family history of cancer, temperate.	12 months.	Failing health, pain frequency, and difficulty in micturition, retention, extensive hard nodular mass in prostatic region.	—	—	—	—	Very pale, sallow, and emaciated, dark complexion. Dismissed.
7	S.R. 732. P.M.R. 126.	1888	70	Bootmaker.	9 months.	Pain and difficulty in micturition, retention of urine, prostate very large, vomiting, hiccough.	Prostate much enlarged, stony hard, all lobes involved, typical scirrhus.	Vesiculæ partly surrounded, bladder, ureters constricted by growth outside bladder.	Iliac and lumbar glands.	—	Obese, acute cystitis, bladder hypertrophy, suppurative nephritis, dilated ureters.
8	C.R., xvii. 116 S.R. 1025.	1890	73	Builder. No serious illness, cancer and phthisis not traced in family.	16 months.	Pain at stool, difficulty in passing motions, prostate a hard, firm mass infiltrating rectum, resistance in lumbar region.	—	—	—	—	Colotomy. No post-mortem examination.
9	C.R. 18/3. S.R. 924. P.M.R. 198.	1891	60	Gasfitter. Cancer and phthisis not traced in family.	2 years.	Frequent micturition, difficulty and pain, hæmaturia, constipation, prostate much enlarged, especially right lobe, enlarged glands both groins.	Hard and fibrous, scirrhus.	Bladder, large growth occluding ureters.	None.	—	Greatly emaciated, right hydronephrosis, left chronic nephritis, ureters dilated.
10	C.R. 163. S.R. 1262.	1896	42	Labourer. Father and brother died of phthisis.	20 months.	Hæmaturia, pain in back, right groin, urethra, perineum, pain on coitus, right side of abdomen rigid, right lobe of prostate enlarged and exquisitely tender, swelling in perineum, temperature raised.	—	—	—	—	No post-mortem examination.

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11	P.M.R. 18. S.R. 696, 1899.	1900	73	Tailor	22 months.	Difficulty in micturition, catheter life.	Prostate uniform, enlargement to size of tangerine orange, firm.	Bladder, round urethral orifice.	Prevertebral glands, kidneys, lungs.	Richly cellular spheroidal cell carcinoma.	Emaciated.
12	O.R. 137. S.R. 98.	1900	68	Master of languages.	14 months.	Difficulty in micturition, hard mass in right groin, smaller enlarged glands on left side, no growth felt in rectum, but extensive resistance over bladder area, emaciation.	Prostate considerably enlarged and hard, small, black, irregular calculus in prostate.	Bladder, corpus cavernosum, seminal vesicle.	Right testicle, inguinal and mesenteric glands.	Richly cellular spheroidal cell carcinoma.	Bladder hypertrophied, right kidney moderate pyonephrosis, right ureter dilated and patent, left kidney granular.
13	S.R. 1103.	1901	70	Ironfounder. Cancer and phthisis not traced in family, smallpox and erysipelas.	8 months.	Retention of urine, catheter life, prostate much enlarged and hard.	—	—	—	Spheroidal cell carcinoma.	Cystotomy and portion removed for examination. Left hospital healed, with catheter.
14	S.R. 1694.	1902	69	Stoker.	15 months.	Decreasing size of stream, complete retention, frequent micturition, pain along urethra on micturition, hæmaturia.	—	—	—	—	Permanent suprapubic fistula established.
15	S.R. 1062.	1903	55	Decorator. Gonorrhœa. Father had difficulty in micturition.	12 years.	Intermittent hæmaturia, frequent micturition, perineal and penile pain, retention of urine, prostate enlarged.	—	—	—	Large spheroidal cell carcinoma, alveolar type.	Suprapubic prostatectomy. Discharged well.
16	S.R. 1549. P.M.R. 229.	1904	64	Farm labourer. Congestion of lungs, temperate, never syphilis.	8 months.	Scalding on micturition, hæmaturia, hypogastric pain and pain at root of penis, frequent micturition, lost weight, prostate enlarged, especially right lobe, very firm, smooth, scar of excised gland in left groin.	Prostate much enlarged, all lobes, especially middle lobe, size of tangerine orange.	Bladder base infiltrated, right ureteral opening involved.	None.	Columnar cell carcinoma.	Fairly nourished, chronic nephritis, moderate right hydronephrosis, dilated right ureter, tumour of prostate explored by incision through abdominal wall, but bladder not opened.

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TABLE OF CASES OF CARCINOMA OF THE PROSTATE—*continued.*

No.	Reference.	Date.	Age	Occupation, Personal and Family History.	Duration of Symptoms.	Prominent Symptoms.	Description of Tumour.	Local Spread.	Metastases.	Microscopical Diagnosis.	Notes.
6	S.R. 1426.	1888	57	Bootmaker. No serious illness, no family history of cancer, temperate.	12 months.	Failing health, pain frequency, and difficulty in micturition, retention, extensive hard nodular mass in prostatic region.	—	—	—	—	Very pale, sallow, and emaciated, dark complexion. Dismissed.
7	S.R. 732. P.M.R. 126.	1888	70	Bootmaker.	9 months.	Pain and difficulty in micturition, retention of urine, prostate very large, vomiting, hiccough.	Prostate much enlarged, stony hard, all lobes involved, typical scirrhus.	Vesiculæ partly surrounded, bladder, ureters constricted by growth outside bladder.	Iliac and lumbar glands.	—	Obese, acute cystitis, bladder hypertrophy, suppurative nephritis, dilated ureters.
8	C.R., xvii. 116 S.R. 1025.	1890	73	Builder. No serious illness, cancer and phthisis not traced in family.	16 months.	Pain at stool, difficulty in passing motions, prostate a hard, firm mass infiltrating rectum, resistance in lumbar region.	—	—	—	—	Colotomy. No post-mortem examination.
9	C.R. 18/3. S.R. 924. P.M.R. 198.	1891	60	Gasfitter. Cancer and phthisis not traced in family.	2 years.	Frequent micturition, difficulty and pain, hæmaturia, constipation, prostate much enlarged, especially right lobe, enlarged glands both groins.	Hard and fibrous, scirrhus.	Bladder, large growth occluding ureters.	None.	—	Greatly emaciated, right hydronephrosis, left chronic nephritis, ureters dilated.
10	C.R. 163. S.R. 1262.	1896	42	Labourer. Father and brother died of phthisis.	20 months.	Hæmaturia, pain in back, right groin, urethra, perineum, pain on coitus, right side of abdomen rigid, right lobe of prostate enlarged and exquisitely tender, swelling in perineum, temperature raised.	—	—	—	—	No post-mortem examination.

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11	P.M.R. 18. S.R. 606, 1899.	1900	73			32 months.	Difficulty in micturition, catheter life.	Prostate uniform, enlargement to size of tangerine orange, firm.	Bladder, round urethral orifice.	Prevertebral glands, kidneys. lungs.	Richly cellular spheroidal cell carcinoma.	Emaciated.
12	O.R. 137. S.R. 99.	1900	68	Master of languages.		14 months.	Difficulty in micturition, hard mass in right groin, smaller enlarged glands on left side, no growth felt in rectum, but extensive resistance over bladder area, emaciation.	Prostate considerably enlarged and hard, small, black, irregular calculus in prostate.	Bladder, corpus cavernosum, seminal vesicle.	Right testicle, inguinal and mesenteric glands.	Richly cellular spheroidal cell carcinoma.	Bladder hypertrophied, right kidney moderate pyonephrosis, right ureter dilated and patent, left kidney granular.
13	S.R. 1103.	1901	70	Ironfounder. Cancer and phthisis not traced in family, smallpox and erysipelas.		8 months.	Retention of urine, catheter life, prostate much enlarged and hard.	—	—	—	Spheroidal cell carcinoma.	Cystotomy and portion removed for examination. Left hospital healed, with catheter.
14	S.R. 1694.	1902	69	Stoker.		15 months.	Decreasing size of stream, complete retention, frequent micturition, pain along urethra on micturition, haematuria.	—	—	—	—	Permanent suprapubic fistula established.
15	S.R. 1082.	1903	55	Decorator. Gonorrhœa. Father had difficulty in micturition.		12 years.	Intermittent haematuria, frequent micturition, perineal and penile pain, retention of urine, prostate enlarged.	—	—	—	Large spheroidal cell carcinoma, alveolar type.	Suprapubic prostatectomy. Discharged well.
16	S.R. 1649. P.M.R. 229.	1904	64	Farm labourer. Congestion of lungs, temperate, never syphilis.		8 months.	Scalding on micturition, hæmaturia, hypogastric pain and pain at root of penis, frequent micturition, lost weight, prostate enlarged, especially right lobe, very firm, smooth, scar of excised gland in left groin.	Prostate much enlarged, all lobes, especially middle lobe, size of tangerine orange.	Bladder base infiltrated, right ureteral opening involved.	None.	Columnar cell carcinoma.	Fairly nourished, chronic nephritis, moderate right hydronephrosis, dilated right ureter, tumour of prostate explored by incision through abdominal wall, but bladder not opened.

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THE X-RAY TREATMENT OF MALIGNANT DISEASE.

By CECIL R. C. LYSTER, M.R.C.S.

The following Paper is divided into two distinct portions. In the first is given a tabular account of all the patients suffering from malignant disease who came under treatment in the Electrical Department of the Hospital during the year 1904, together with certain remarks where these appear necessary. The second portion is more general, and deals with the results of personal experience.

Out-Patients suffering from Cancer who came under treatment in the Electrical Department during the year 1904.

Note.—*The exposure given has usually been for ten minutes, with the tube at eight inches from the surface under treatment, the tube being excited by the discharge from a twelve-inch coil with a current of five ampères. These conditions, however, were frequently altered. Diagnosis rests on macroscopic grounds alone.*

RODENT CANCER.

Name, Age, Date.	Situation.	Duration on Admission.	Remarks.
1. William F— 84 19.2.04.	On bridge of nose and R. cartilage.	7 months	Treatment discontinued by patient Nov. 23rd. Ulcer ¼ original size.
2. Edward F— 53 2.2.04.	Left side of nose, size of sixpence.	12 years	Attendance very irregular. Ulcer still exists, smaller and healthy.
3. William H— 62 4.3.04.	Whole right side of nose and part of upper lip. Recurrence after operation.	12 years	Ulceration has healed.
4. Emily F— 56 2.4.04.	On bridge of nose and right side.	Recent	Healed well. Oct. 3rd, 1904, no sign of disease.

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Name, Age, Date.	Situation.	Duration on Admission.	Remarks.
5. Edward C— 64 16.3.04.	Left lower eyelid and side of nose.	Many years	Healing slowly. Exposure changed Dec. 8th, 1904. Tube with lower vacuum used. No change in healing.
6. Annie S— 42 4.5.04.	Upper lip; whole lip gone.	21 years	Edges of ulcer cleaned by 1st June. Now no ulceration.
7. Julia R— 46 5.5.04.	Left breast above nipple, 4 inches across, 3 inches above downwards. Breast appears to have been entirely removed by disease.	8 years	Steady improvement up to Jan. 1905.
8. James H— 53 30.5.04.	Ulcer extends from outside of left eye to ear, deep and foul.	4 years	X-rays caused such pain immediately after application that radium was tried (10,000 activities for 5 minutes). Pain still continued, and treatment was discontinued on July 4th, 1904. The wound had not improved.
9. Rhoda B— 65 11.6.04.	Nose and upper lip	4 years	No visible improvement; discontinued Aug. 10th, 1904.
10. Walter H— 42 13.7.04.	Right ala of nose destroyed.	—	Steady improvement; nearly healed, but back to the Hospital Aug. 10th.
11. Julia C— 76 20.6.04.	Inner side of right eye, lower lid.	Long duration.	Slow, but steady healing; not yet quite healed.
12. Louisa G— 56 29.9.04.	Outer side of right eye.	9 years	Only attended twice.
13. Louis R— 42 25.10.04.	Right lower eyelid	2 years	Healed well, Jan. 10th, 1905.
14. Ann D— 44 3.11.04.	Left lower eyelid ...	2 years	Jan. 31st, 1905. Quite well.
15. Eliza S— 65 18.7.04.	Left eyelid ...	1½ years	Admitted as in-patient Nov. 14th.
16. John P— 50 7.10.04.	Bridge and left side of nose.	2 years	Ulceration healed well, and thickening disappeared; now quite well.

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SARCOMA.

Name, Age, Date.	Situation.	Duration on Admission.	Remarks.
17. John A— 58 3.0.04.	Sarcoma right side lower jaw.	—	Remains stationary. There are no glands involved.
18. William H— 47 3.10.04.	Sarcoma, right tonsil extended to whole back of mouth.	1½ years	Still under treatment. Disease increasing. Patient feels no pain and less discomfort.
19. Elizabeth C— 53 3.10.04.	Endothelioma (microscopic) of sternum.	—	No change to Dec. 12th. Not attended since.

CANCER.

20. Charles P— 61 18.1.04.	Extensive cancer of tongue and floor of mouth, glands in neck; not been operated on.	—	Pain a prominent symptom; this was relieved, but the ulceration extended, and patient was unable to attend after March 7th.
21. Thomas S— 51 29.3.04.	Mass of ulcerated growth in left side of neck, secondary to disease of tongue.	2 years	Discontinued April 15th. No improvement.
22. James S— 60 11.4.04.	Recurrence in floor of mouth, after removal of tongue in Jan. 1904. Glands affected.	1½ years	Continued till June 6th. No improvement.
23. Dora G— 65 9.5.04.	Extensive infiltration of buttocks from anus.	1 year	No improvement.
24. Charles C— 54. 9.5.04.	Disease of tongue.	—	Did not ease pain.
25. Edward H— 55 16.5.04.	Excision of tongue, Feb. 1903. Recurrence in glands of neck and floor of mouth.	2 years	——
26. Henry H 43 2.6.04.	Cancerous ulcer, 1½in. by 1in., in region of fifth dorsal vertebra.	6 years	The ulcer healed slowly, and by the end of Nov. 1904 was healed; it then broke down again. On Dec. 16th was again healing. Jan. 23rd, 1905, it broke down again, possibly due to action of rays from a tube with lower vacuum. It is now healed again.

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Name, Age, Date.	Situation.	Duration on Admission.	Remarks.
27. Charles M— 41 1.9.04.	Cancerous ulcer of tongue. Deposit in glands in neck.	1 year	No improvement.
28. Emily S— 39 14.1.04.	Extensive ulceration right side. Recurrence after removal of right breast. Nodules in upper flap.	—	Ulcer cleaning when patient discontinued treatment.
29. Anne B— 57 18.1.04.	Secondary deposit in scar and lower flap and in axilla after removal of breast.	5½ years	Pain relieved. Before July there was no alteration in size of nodules. Weight had decreased from 13 st. 4 lb. to 12 st. 9 lb. From July there was a steady decrease in size of nodules; some have disappeared, others are very small. Weight has increased to 13 st. 2 lb. and remains steady.
30. Annie R— 48 8.2.04.	Recurrent nodules in scar after removal of right breast. No enlargement of glands.	—	In this case the nodules disappeared, and on July 25th, 1904, there was nothing to be felt.
31. May B— 52 8.2.04.	Large recurrent mass fixed to chest wall. Left side ulcerated. Glands in neck enlarged.	"Some years."	Complained of great difficulty in breathing. Treatment discontinued.
32. Sarah C— 59 8.2.04.	Large mass in scar and under left axilla. Abscess in axilla recently opened. No glands about clavicle. Arm œdematous. Ulcerating.	2 years	In this case the weight increased from 9 st. to 9 st. 11 lb. and still remains at that. The ulceration slowly healed, and the mass diminished in size. Arm less swollen. In Jan. 1905 glands were noticed in neck. No pain since commencement of treatment.
33. Evelyn H— 36 14.3.04.	Both breasts were involved. No operation had been performed. No glands could be felt.	R. 4 years L. 1½ years	Distinct decrease in size of both breasts was noticed in beginning of May; improvement continued till August, when patient's health began to fail. Two months later death ensued with pulmonary symptoms.

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Name, Age, Date.	Situation.	Duration on Admission.	Remarks.
34. Annie C— 53 19.3.04.	Recurrent disease in scar after removal of right breast, numerous nodules in skin and fixed to chest wall. Enlarged glands in neck.	1½ years	Glands in neck steadily increased in size. No alteration in the growth. Weight decreased from 8 st. 7 lb. to 7 st. 10 lb. Treatment discontinued July 18th.
35. Mabel R— 38 21.4.04.	Recurrence in the scar after removal of right breast, in the skin above and below scar and in the axilla.	2½ years	Patient did not attend.
36. Caroline S— 54 2.5.04.	Extensive infiltration of right breast and skin up to clavicle. Enlarged glands in neck.	1½ years	The disease increased steadily, and the glands became larger. Length of exposure was doubled in July, but there was no improvement. Treatment continued till December.
37. Frances B— 74 2.5.04.	Right breast was extremely infiltrated and ulcerated. No glands to be felt.	6 years	In this case the ulcer quickly cleaned, healed, and the growth became free and small; no pain, and the weight remained at 9 st. Death. Cf. This vol. p, 21, No. 104.
38. Sarah F— 58 9.5.04.	Right breast hard and ulcerated, fixed to chest wall. No glands to be felt.	7 years	The ulcer cleaned, and has steadily healed; the growth is not one half the size, and is not so adherent to the chest wall. No pain.
39. Elizabeth M— 48 6.6.04.	Cancer of the right breast, with very extensive ulceration.	8 months	The disease extending rapidly.
40. Susan C— 43 6.6.04.	Uterus	1½ years	Refused further treatment.
41. Bessie M — 58 16.6.04.	Cancer of the left breast, with extensive ulceration.	2 years	The growth and ulceration extended rapidly, and treatment was discontinued Sept. 24th, 1904.
42. Jane R— 49 4.8.04.	Cancer of the right breast.	"Several years."	The patient lived some distance from town, and was so fatigued with the journey that treatment was discontinued Aug. 9th.

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Name, Age, Date.	Situation.	Duration on Admission.	Remarks.
43. Elizabeth E. 68 30.7.04.	Cancer of the left breast fixed to skin and chest wall. No ulceration and no glands to be felt.	—	The mass has continued to get smaller, and is not so firmly fixed. General condition improved. Weight risen from 6 st. 6 lb. to 6 st. 12 lb.
44. Maria Anne B. 56 8.8.04.	Infiltration of left breast, with small ulceration fixed to chest. No glands.	8 months	The ulceration has healed, and the breast is smaller, softer, and not so fixed.
45. Harriet M— 68 26.10.04.	Extensive recurrence and ulceration in the scar after removal of left breast; enlarged glands in neck and axilla; arm swollen.	2 years	Growth in breast and axilla has decreased, and ulceration healed. Glands in neck have increased in size, and the œdema of arm is increasing. Considerable pain in arm.
46. Sophia H— 44 5.10.04.	Left breast. Axillary glands.	4 years	Admitted as in-patient Feb. 1905.

PART II.

The treatment of carcinoma by means of X-rays is still in quite an experimental stage. The number of cases in which (*a*) cutaneous and subcutaneous nodules disappear or (*b*) larger masses of malignant growth not only cease to enlarge but unquestionably decrease in size, impresses on one the belief that if we give the right exposure of X-rays we can retard the disease. But there is a larger number of cases in which, although the disease appears to be well in reach of the action of the rays, we fail to produce any effect on the growth, although exposure is carried to the utmost limit consistent with safety. Moreover, we cannot indicate with certainty which cases are likely to do well and which are not.

Broadly speaking, no case on which it is possible for an operation to be performed should be subjected to the rays. For the length of time which must elapse, even in a favourable case, before a result is produced is more than counterbalanced by the disadvantage of delay to the patient in case that satisfactory result is not attained.

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Subject to the proviso in the last paragraph, the treatment in one or other form may be applied to all cases of carcinoma. Nevertheless, certain conditions are pre-eminently suitable.

Pain.—Cases in which there is much pain, not due to implication of a nerve trunk, are generally relieved, even when the disease is situated a considerable distance from the surface of the body.

Ulceration.—Ulcerated surfaces become clean and in many instances heal, either entirely or partially. The thickened skin and tissues surrounding superficial malignant growths often become soft and resume their normal state.

Nevertheless, beneficial results from use of the rays cannot be expected in every case. In some instances ulceration is so rapid (probably owing to that inferior local circulation and poor general nutrition which usually is present) that even when the amperage is raised to the utmost limit of safety no attempt at healing is recognisable. And this, too, although a far lower amperage would lead to eminently satisfactory results in another case, where the ulcer was more of a chronic type, and the general and local conditions were better. Any attempt to push matters in cases of the first description only results in aggravating the ulceration as well as in causing the patient great pain.

The type of growth.—The action of X-rays varies on different kinds of malignant disease.

In rodent cancer, when not of too long duration, it seems to give the best results. The ulcerated surface cleans and rapidly becomes covered by a new epithelium. The subcutaneous thickening disappears more slowly, it is true, but in a number of cases none the less completely. Where the ulcer is of long standing, the healing process seems to progress well at first; sometimes, indeed, complete cicatrization may occur. But in most cases, after a time, even during the course of a treatment which is undergoing no recognisable alteration, either the remaining portion of the ulcer does not respond in the same way to the action of the X-rays as before, or else the growth breaks down again. In spite of having experimented in such cases with tubes of different

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degrees of hardness and softness, with different lengths of exposure, with different frequencies of exposure, and different amperages, I can so far suggest no explanation of what is an undoubted fact.

Recurrences after removal of carcinoma of the breast where secondary nodules are confined to the scar, or the surrounding skin and subcutaneous tissues, generally give good results. No difference can be recognised in the results according to their early or late appearance after the primary operation, but *cæteris paribus* hard recurrent nodules yield better to X-ray treatment than those which are soft.

Carcinoma of the tongue and mouth.—Starting from the original proposition that no case should be subjected to the action of the rays which is still operable, we are reduced, in cases of the present category, to instances of local recurrence or of secondary deposit in the submaxillary or other glands. In such cases growth is generally so rapid that we are unable to give a sufficiently long exposure to X-rays without damaging the surrounding healthy tissue. Consequently these cases conform to the type already mentioned in which rapid ulceration is a marked characteristic. It is important to note, however, that in many of them moderate treatment has led to marked relief of pain. In a very few the ulcerated surface has healed and the extension of the growth has been retarded.

Carcinoma of the rectum.—The following case illustrates the decrease or disappearance of malignant tissue in the deeper parts of the body.

Male, aged 45: In May 1903 colotomy, followed by Kraske's operation, was performed; the wound healed well. In December 1903 the patient came to the Hospital with an ulcerated nodule in the scar as large as a hen's egg, and surrounded by general cancerous infiltration of the tissues. The growth was exposed to X-rays 3 times a week. No reaction took place for 4 weeks, but after this there was a steady improvement, the ulcer cleaning and the growth diminishing in size. By April 1904 there was so marked an improvement that the patient was able to resume part of his usual occupation as a tax-collector. In June 1904 there was apparently no growth left, and the ulceration had nearly healed up. Up

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to the present time (March 1905) there has been no return of disease and the ulceration has been healed some months. The patient is well and able to do his work.

Supraclavicular glands.—According to 6 cases in which the point has been specially observed, secondary deposit in glands in the neck seems to be less affected by the action of the rays than when the deposit is in the glands situated below the clavicle. The following case is a striking instance.

Female, aged 53: The right breast was removed for carcinoma and the axilla was cleared out 3 years before coming under electrical treatment. Recurrence took place 16 months after the operation in the upper flap, in the axilla, and in glands under the clavicle. There were considerable pain and œdema of the arm. Treatment by X-rays was commenced in January 1903, and an exposure was given of 16 minutes 3 times a week to the action of rays produced in a tube with a high vacuum. The reaction was never very marked, but the pain at once diminished and the subcutaneous nodules on the chest wall become smaller, while the œdema of the arm disappeared. In February 1904 a small gland was noticed in the neck above the clavicle. In December 1904 there were no subcutaneous nodules present, but the glands in the neck above the clavicle had increased in size, and the disease had become so extensive in this region by January 1905 that further treatment was discontinued. In this case the patient was enabled to resume her ordinary housework and continue it for a year and a half with very little inconvenience and no pain.

Radium.—The treatment of carcinoma by means of radium emanations has not been successful. The very small quantity of radium available has made it quite impossible to deal with any but the smallest rodent ulcers, which could have been excised, or treated equally well with X-rays. When the salt of radium is nearly pure, if applied, it gives rise to dermatitis very readily. This may possibly be due to the free electrons discharged during its action.* Radium salts of lower activity seem to have little or no effect. Until we can get a

* I am at present conducting experiments to determine, if possible, whether the similar action of X-rays is due to the presence of free electrons.

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quantity of nearly pure radium and are able to apply it over a larger area, it is impossible to form any opinion concerning its action on cancer.

The results of my experiments* in the use of the Becquerel rays emitted by pitchblende in the form of a screen have not been successful. The small quantity and low penetrating power of these rays necessitated such a prolonged exposure that the hard screen caused much discomfort when kept in contact with the tender or ulcerated surface of a malignant growth. In two cases redness and slight dermatitis supervened, and I felt that until some better means of application could be found it was useless continuing these experiments.

Recent modifications.—Of recent improvements in the apparatus used to produce X-rays, the most important are the water-cooled anode and regulating tube. By using the regulating tube the vacuum can be maintained for a longer period in its original condition. In this way the gradual hardening of the tube and consequent diminution in the quantity of rays is obviated. By means of the water-cooled anode a much larger amount of current can be passed into the tube without danger of super-heating the anode. Nevertheless, we are still dependent on a glass tube, the vacuum in which is constantly varying, and the quantity and quality of X-rays varying with it.

A Mille-Amperemeter has been introduced to use in the secondary circuit of the coil with a view of measuring more accurately the current passing through the tube; this it does as regards the quantity, but it takes no account of the voltage, and for this reason it might seriously mislead one as to the quantity of X-rays emitted from one tube. This could only be indicated by a watt reading of amperes and volts.

Nevertheless, we are still in need of a means for accurately measuring X-rays. One tube, with a definite discharge from a coil, will give rays of highly penetrating nature, and another with the same discharge will give rays with a much lower penetrating power; also the same tube will vary according to the increase or decrease in vacuum in the quality of rays emitted.

* "Arch. Middlesex Hosp." vol. i. p. 93.

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We also need some means by which we can be certain that the X-rays are not accompanied by negative electrons. Every now and then we come across a tube the rays from which, even with the smallest exposure, cause an acute dermatitis totally unlike the ordinary reaction. This dermatitis, as is well known, can be produced by any tube if too great an amperage is used in the coil; but in the tubes to which reference is now being made it seems possible that some of the electrons from the cathode stream escape through the glass of the tube and act on the skin much in the same way as the free electrons from radium.

To summarise:—

(1) Treatment of malignant growths by X-rays is only local; it does not in any way affect the growth of secondary deposits in parts of the body other than that under exposure.

(2) Without injury to the skin it is impossible to administer a sufficiently strong exposure to modify growth in the viscera. So far as concerns disease situated in any of the deeper tissues X-rays are not applicable as used at present, except in cases where there is distinct relief of pain. An innocuous exposure will, however, frequently cause relief of deep-seated pain.

In the cases where the disease is superficial, treatment by X-rays almost always relieves pain, retards growth, produces retrogressive changes, and enables many patients to resume their ordinary life.

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A MICROSCOPIC STUDY OF THE PARIETAL DISSEMINATION OF MAMMARY CARCINOMA.

By W. SAMPSON HANDLEY, M.S. (Lond.), F.R.C.S.

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In a paper dealing with the various parietal metastases in breast cancer, which appeared in the "Archives of The Middlesex Hospital," vol. iii., 1904, I arrived at the following conclusions:—

(1) The study of secondary growths in the skin and subcutaneous fat, and in the bones, affords clear evidence of a slowly progressive, centrifugal, quasi-serpiginous spread of breast cancer in the parietes, in continuity with the primary growth, and independent of transport by the lymph or blood stream. This conclusion was based on the facts that (*a*) secondary growths are usually first observed in the immediate neighbourhood of the primary growth; (*b*) though growth gradually spreads centrifugally from the primary focus the distal halves of the limbs enjoy a practical immunity from secondary deposits.

(2) The scattered and isolated character of the deposits in the skin and bones indicates that it is not along these layers that the growth primarily spreads.

(3) A study of the results of operation where (*a*) much skin and fascia, (*b*) less skin and more fascia, are removed strongly suggests that parietal extension does not take place primarily along the skin, but along the deep fascia, with secondary lateral offshoots towards the surface as subcutaneous nodules on the one hand, and towards the deeper tissues as bone and muscle on the other.

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It is evident that these conclusions are only provisional, since they are derived merely from macroscopic and statistical evidence. It seems that the facts would be best explained by the continuous centrifugal growth of cancer along the meshes of the deep fascial lymphatic plexus into which many, if not all, of the breast lymphatics drain, and from which the trunks arise that convey lymph from the parietes to the axillary or to the inguinal glands. But though when present in its highest degree this process, to which I have ventured to apply the term "permeation," seems traceable by the characteristic distribution of the resulting naked eye metastases in the skin and bones, more frequently macroscopic evidence is dubious or wanting.

It was necessary, therefore, to test the hypothesis of centrifugal permeation by the microscope. This has been done by the examination of strips of the parietal tissues, radiating from the edge of the primary growth. In two cases, in order to minimise mutilation of the body, the strip examined was a median ventral strip in the line of the usual post-mortem incision. Though not accurately radial to the growth such a strip is sufficiently so for practical purposes. The layers included in the strips were skin, subcutaneous fat, deep fascia, and a superficial layer of muscle. From each strip, after fixation for a few days in 1 per cent. formalin to prevent separation of the overlying tissues from the deep fascia and muscles, a thinner strip, about $\frac{1}{8}$ inch thick, was cut, in a plane vertical to the skin. In order to make this section as accurately as possible the strip was frozen hard before cutting.

The thin strip thus obtained was divided by transverse cuts into a number of blocks of suitable size. The end nearest the growth was marked in each block by a small cut in the skin surface. The pieces were then transferred, in order, to numbered bottles, hardened in alcohol, and embedded in paraffin. The resulting series of sections was stained with hæmatoxylin and eosin, and a microscopic view of the whole length of the original strip was thus obtained.

In one case (case ii.) a continuous series of from thirty to fifty sections was mounted from nearly every block of the

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two strips examined. In this case, therefore, over 500 microscopical sections had to be prepared and examined.

Five non-consecutive cases, now to be described, were more or less completely dealt with in this manner.

CASE I.

On the thorax in the region of the right breast is an ulcerated tumour as large as an orange. It is surrounded by isolated hard nodules, which occupy the axilla (under the Pectoralis major), and fill up the right axilla itself, where they form a mass pressing on the axillary vein, and causing œdema of the arm.

Similar nodules are found in the left breast. The skin over the sternum between the breasts also shows a few small subcutaneous nodules. One large nodule is situated under the left pectoral muscle, but there are no enlarged glands in the left axilla. The supra-clavicular glands are palpable on the right side. There are no nodules on the skin of the back, abdomen, &c.

Three ribs beneath the right breast are completely infiltrated, and the right pleura shows numerous white hard nodules, especially on its parietal portion.

There are numerous nodules on the posterior aspect of the sternum. The right lung shows a few hard nodules; the left lung also, but to a less extent.

The liver presents several secondary nodules on its surface near the round ligament.

The parietal strip examined was a median ventral one, extending from 25 mm. below the suprasternal notch to a point 60 mm. above the umbilicus.

A slice 3 mm. thick, hardened and stained in Orth's fluid and cleared in xylol*, demonstrated very clearly that the growth was extending downwards, macroscopically at any rate, not along the skin but along the plane of the deep fascia.

* For a description of this method, which in my hands has given better results than Stiles' nitric acid method, see "Archives of The Middlesex Hospital," vol. iii., p. 35.

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DETAILED MICROSCOPICAL EXAMINATION OF CASE I.

Taking the level of the umbilicus as a fixed point and travelling upwards along the strip, we will now describe the conditions found at each level.

The distances are expressed in millimetres above the umbilicus. The foci between levels 160 and 188 mm. are shown in Fig. 1 under a low magnification.

(1) *Level* 0–60 *mm.*—Tissues not examined.

(2) *Level* 60 *to* 160 *mm.*—Tissues found entirely free from Cancer.

Zone of Fascial Permeation, Inflammatory Reaction Absent.

(See p. 218.)

(3) *Level* 160 *mm.*—Two minute lymphatics each about 60μ in diameter, containing groups of cancer cells, lying upon the anterior layer of the Rectus sheath (see Fig. 3). There are no leucocytes either within or around the invaded lymphatics. A normal minute blood vessel lies near them.

(4) *Level* 161·2 *mm.*—A gaping space lined by endothelium and situated upon the deep fascia. By comparison with other sections it is clear that this is a lymphatic from which a group of cancer cells has fallen out.

(5) *Level* 166 *mm.*—Two lymphatics filled by cancer cells in the deepest layer of the subcutaneous tissue, lying near a normal artery. Close to these are two minute nodules of cancer, the largest ·8 mm. in diameter.

(6) *Level* 167 *mm.*—Two lymphatics, respectively 160 and 80μ in diameter, lying on the deep fascia, and filled by cancer cells. There are no leucocytes in the neighbourhood. The cancer cells in the larger vessel, except those lying next the endothelium, are swollen, degenerate and highly refractile, and stain imperfectly. The lines of separation between adjacent cancer cells are very sharply defined.

(7) *Level* 172·6 *mm.*—Lying on the Rectus sheath close to normal blood vessels in which red corpuscles can be seen, is a group of three minute lymphatics, the largest about 70μ in diameter, each containing groups of cancer cells. Close to these on the surface of the fascia is a minute cancer nodule

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about ·25 mm. in diameter. The appearances suggest that this originated from the rupture of a lymphatic by the growing mass of cancer cells within it. Only very few leucocytes are present near the invaded tissues.

(8) *Level* 175·6 *mm.*—An oval space 250μ in mean diameter, lying on the Rectus sheath, and apparently lined by endothelium. It is filled by cancer cells which towards the centre are swollen, hyaline, degenerate, and polygonal from mutual pressure, though their nuclei still stain fairly well. The peripheral layer of cancer cells is not degenerate. The space appears to be a lymphatic distended by cancer cells, but not to the point of rupture. On one side of the permeated lymphatic is a small aggregation of leucocytes.

(9) *Level* 176·9 *mm.*—On the surface of the Rectus sheath is a lymphatic, 140μ in diameter, with a thin wall consisting practically only of endothelium with well-stained nuclei. Some of the cells in the centre of the group are beginning to degenerate. Near the lymphatic is a group of normal minute blood vessels, round which are a few emigrated leucocytes. There are no leucocytes in the immediate neighbourhood of the permeated lymphatic.

(10) *Level* 177·3 *mm.*—On the Rectus sheath is a lymphatic 90μ in diameter, lined by definite endothelium, and filled by cancer cells, which have somewhat shrunk away from its walls. Leading from it right through the Rectus sheath to its muscular aspect is a minute vessel lined by endothelium, evidently a branch lymphatic, into which growth has not penetrated. There are no leucocytes near the permeated lymphatic (Fig. 4).

(11) *Level* 178·6 *mm.*—A small lymphatic full of cancer cells lying on the anterior layer of the Rectus sheath.

(12) *Level* 182·6 *mm.*—Oval section of an endothelium-lined lymphatic, 110μ in diameter, lying upon the anterior layer of the Rectus sheath, and filled by cancer cells that stain well and show no signs of degeneration. Near it is a group of minute blood vessels, around which are about a dozen emigrated leucocytes.

(13) *Level* 182·9 *mm.*—An endothelium-lined lymphatic, 150μ in diameter, lying on the Rectus sheath, and distended by cancer cells. The central cells are degenerate. At one side

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the lymphatic vessel has apparently ruptured, and the cancer cells are beginning to infiltrate the adjacent tissue. There is no leucocytosis.

Zone of Fascial Permeation, Perilymphatic Leucocytosis present.

(14) *Level* 184·5 *mm.*—On the anterior surface of the Rectus sheath is an oval empty space 450μ in diameter, lined only by rough fibrous tissue, though on one side there appear to be traces of endothelium. It possesses no proper wall of its own, and contains only a few scattered red corpuscles, and a group of cancer cells adherent to its wall at one point. On the deep aspect of this space the Rectus sheath is infiltrated by groups of cancer cells nearly to its muscular surface. The blood vessels in the neighbourhood are crowded with leucocytes, and there is a commencing leucocytic invasion of the carcinomatous cell groups.

The appearances here may, but probably do not, represent the invasion of a vein by cancer. The large space has no definite coats, and is almost certainly a lymphatic which has ruptured owing to hyper-distension by cancer cells (cf. Fig. 8). This rupture is associated with slight traumatic hæmorrhage, and with inflammatory reaction which encapsules the cancer cells. Definite inflammatory reaction here shows itself for the first time.

(15) *Level* 185·3 *mm.*—Diffuse infiltration of the Rectus sheath nearly to its deep surface by cancer cells lying singly or in groups. They stain badly, are surrounded by a crowd of leucocytes, and are apparently being destroyed.

(16) *Level* 186 *mm.*—A space 500μ in diameter, lying on the anterior layer of the Rectus sheath, exactly similar to that described at level 184·5 mm. It contains, however, in addition to some few red blood corpuscles, a larger group of degenerate cancer cells. The leucocytic reaction in the surrounding tissues (which as in the former case are infiltrated by groups of cancer cells) is rather more marked. It is noticeable, too, that many of the cancer cells, even in the smaller groups, have completely degenerated into a hyaline unstained material.

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(17) *Level* 187 *mm.*—Two endothelium-lined lymphatics, each about 125μ in diameter, on the superficial aspect of the Rectus sheath, permeated by somewhat degenerate cancer cells. A slight hæmorrhage has taken place into one of them, though at the level of the section no rupture can be seen. A few isolated cancer cells are present in the neighbouring tissues, together with some emigrated leucocytes.

(18) *Level* 188·3 *mm.*—A large oval space, 1·5 mm. in its long diameter, possessing a definite but very thin wall, which though in places showing traces of an endothelial lining, seems to consist chiefly of young nucleated fibrous tissue mixed with cancer cells. This space may possibly be an invaded vein, but almost certainly it represents an invaded and ruptured lymphatic, with a wall of newly-formed fibrous stroma. For in a nodule of cancer situated in the muscle higher up there is an exactly similar space lying quite close to an artery and vein, neither of which is invaded by growth.

The space contains a mass of cancer cells, now somewhat shrunken, which, no doubt, during life completely filled it. There are, however, here and there around the mass of cancer cells some altered red blood corpuscles. The peripheral cells of the cancerous mass are vigorous and stain well, while the central cells are swollen and hyaline, and in places entirely converted into an unstained granular material. There is a slight leucocytic reaction in the tissues round the space.

(It should be noted that up to this point cancer occurs only in, upon, or just over, the deep fascia, and has not invaded either skin or muscle.)

Zone of Perilymphatic Fibrosis, with early Nodular Deposits.

(19) *Level* 188·5 *mm.*—In the subcutaneous tissue is an oval annular area of fibrous tissue, about 125μ in diameter, enclosing cellular débris. In the centre of this débris are a few cells which show all the characters of carcinomatous epithelium.

(20) *Level* 189·5 *mm.*—Lying just beneath, but not actually reaching the surface of the transversely-cut muscle (pectoralis) seen at this level, there is a nodule 2 mm. in diameter. It is

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bluntly conical in shape, with its apex directed towards the deep fascia, and is connected therewith by a fibrous septum, in which some microscopic sections show a lymphatic containing a mass of degenerate cancer cells.

(21) *Level* 190·1 *mm.*—In the subcutaneous tissues over the deep fascia at this level there is a small normal artery and vein. Touching them is a small circular area of concentrally arranged fibrous tissue, enclosing some cellular débris.

(22) *Level* 190·1 *mm. to* 196·3 *mm.*—In this part of its length the subcutaneous tissue down to the deep fascia shows at short intervals, especially along its fibrous septa, circular, oval, and strap-shaped areas of fibrous tissue. Many of these areas enclose either stained cells, sometimes recognisable as cancer cells, or they contain cellular débris. Some of the areas consist entirely of fibrous tissue. The muscle is normal, except for one or two lymphatics filled with cancer cells.

(23) *Level* 196·3 *mm.*—At this level the skin shows cancer for the first time. There are two spaces in the dermis, lined by endothelium, which contain degenerate cancerous epithelium. Near them are a few cancer cells lying interstitially. From this point for 6 mm. upwards the deeper layer of the dermis is more or less invaded by growth which is partly intra-lymphatic, partly interstitial. The appearances in the subcutaneous tissue are unchanged. Some of the fibrous areas in it have a gland-like appearance, and may possibly be outlying lobules of breast tissue, but this is certainly not the case with most of them.

(24) *Level* 199 *mm.*—A large cancer-filled lymphatic in the deep subcutaneous tissue close to the fascia.

Zone of Nodules, Permeated Lymphatics Destroyed.

(25) *Level* 199 *mm. to* 224 *mm.*—In this region the cancer process is so far advanced that it becomes needless to trace it microscopically. As one passes upwards, the cancerous masses, becoming larger, at length involve all the layers indiscriminately. Permeated lymphatics can still be seen here and there among the nodular and often apparently isolated deposits.

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It is noticeable that macroscopic nodules in the muscle occur much further down, *i.e.* further away from the growth, than do macroscopic nodules invading the skin.

(26) *Level* 224 *mm.*—We have now arrived at the approximate level of the nipple and of the primary growth. Near this point is a skin nodule about 1 mm. in diameter, the only one visible to the naked eye in this strip examined. Since the strip, though reaching higher than the primary growth, did not at its upper limit extend as far as the microscopic growing edge of the carcinoma, it is useless to trace it further.

SUMMARY OF MICROSCOPIC EXAMINATION OF CASE I.

The microscopic growing edge of the cancer reaches to a point about 1½ inches below the ensiform cartilage. Below this point the tissues are quite free from growth, while above it they show foci of cancer at short and fairly regular intervals. The lower limit of the pectoral fascia has not in any way barred the downward course of the growth. At one point the cancer has penetrated the anterior layer of the rectus sheath nearly to its deep surface, Had the section passed through the linea alba, cancer cells would doubtless at this level have been seen in ominous proximity to the subperitoneal fat and peritoneum.*

For a breadth of over 30 mm. the microscopic margin of the carcinoma lies exclusively in the plane where the deep fascia joins the overlying fat (see Fig. 1).

The microscopic growing edge, traced from the periphery towards the primary growth, presents the following zones, each of which merges gradually into the zone on either side of it:—

(1) *Zone of Permeation of the Deep Fascial Lymphatic Plexus.*—This zone presents two subdivisions. In its peripheral portion inflammatory reaction is absent. The lymphatics forming the plexus are seen at short intervals as spaces lined by endothelium and containing cancer cells in an active condition. The lymphatics are not distended, and

* The subject of "Epigastric Invasion of the Abdomen" is dealt with at length in my Astley Cooper Prize Essay, shortly to be published in the Guy's Hospital Reports.

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there are no leucocytes around them. In the proximal portion of the zone of permeation the lymphatics show increasing distension by the growing cancer cells, which themselves are undergoing degeneration from the increased pressure produced by their proliferation. Around the invaded lymphatics are seen collections of inflammatory round cells. Still nearer to the inner margin of the zone are seen large spaces containing cancer cells and a few red blood corpuscles. It will be shown later that these spaces are formed by the rupture of the distended lymphatics.

(2) *Zone of Fibrosis around the Permeated Lymphatics, (Perilymphatic Fibrosis), with Destruction of the Cancer Cells contained in them.*—In consequence of this process the adjoining layers—first the muscle, and later the skin—show commencing nodular invasion, which is brought about in a way to be presently described.

(3) *Zone of Discrete Nodular Deposits in all the Parietal Layers.*—As the primary growth is approached these deposits become more massive and numerous. The sporadic distribution which they often seem to show results from fibrous obliteration of the permeated lymphatics which formed the lines of communication with the primary growth. In this zone the cancer process is so far advanced that its earlier stages can only be traced inferentially from the appearances nearer the growing edge.

Beyond this zone is the primary growth proper, which may be defined as the region of interstitial infiltration round the original focus.

CASE II.

In the site of the right breast was a fungating crateriform mass as large as a man's hand, extending from the second down to the sixth rib, and obliquely from the parasternal line to the anterior fold of the right axilla. In continuity with the tumour some glands were found in the right axilla, and there was marked œdema of the right arm.

Independently of the first tumour, the left mamma was enlarged (probably secondarily) and showed a conical tumour adherent to the skin. Several cutaneous nodules of the size

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of a pea were scattered round the principal mass on the left side of the thorax, but there was no ulceration present. The left axillary glands were involved, but there was no œdema of the left arm. There was an enlarged gland of the size of a walnut above the right clavicle. The right pleura showed some white prominences at the level of the right breast, where two ribs and the intervening muscles were completely invaded by the growth. Posteriorly there were some small scattered growths on the parietal pleura, especially in its lower part.

The lumbar glands were not enlarged, but were white on section, as if containing new growth. One portal gland the size of a hazel nut appeared distinctly malignant. Some malignant deposit occupied the anterior border of the right lobe of the liver, and several nodules were scattered through its substance.

Two parietal strips were taken from this case, one running outwards along the arm, the other downwards and backwards into the loin; so as to institute a comparison of two radial sections of the growing edge chosen at random.

The proximal portion of these strips presented to the naked eye an almost continuous series of subcutaneous nodules lying along the line of junction of the dermis with the subcutaneous fat, and infiltrating the overlying dermis. The deeper tissues appeared to be quite free from growth. It seemed evident, *prima facie*, that the growth was spreading along the plane of the deep cutaneous plexus. This fact lent special interest to the case, since I had previously met with no evidence to support the belief that breast cancer spreads along this hypothetical plexus, whose existence is strongly denied by Sappey.

STRIP A.—EXTENDING FOR 90 MM. FROM THE OUTER EDGE OF THE ULCERATED MASS OF GROWTH AND DOWNWARDS ALONG THE RIGHT ARM.

The strip was divided into six blocks, four of which were cut in series. About 250 sections were in all examined.

Skin.—The condition of the skin need not be described in detail. It is invaded more or less continuously along its

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whole length by confluent nodules which diminish in size and become microsopic, until at 84 mm. distance from the edge of the malignant ulcer, and 1 mm. beyond the microscopic edge of the cancer in the deep fascia, the last minute nodule is seen. Beyond this point the skin is free from growth.

Along the proximal five-sixths of the strip the skin which intervenes between neighbouring skin nodules shows lymphatic and interstitial invasion by cancer cells. The distal 8 mm. of the invaded portion of skin is free from cancer, except for two isolated skin nodules at the deep aspect of the dermis.

Subcutaneous Tissues.—There are in the subcutaneous tissues a few nodules visible to the naked eye. Permeated lymphatics are to be seen here and there, generally close to the nodules.

Deep Fascia.—All the foci of cancerous growth found in the deep fascia are included in the following description. The figures represent distances from the ulcerated edge of the growth.

Zone of Nodules, Permeated Fascial Lymphatics partially or completely Fibrosed.

0 *to* 10 *mm.*—Fascia missing from the strip.

27·5 *mm.*—Lying upon the fascia are a small artery and vein, the former surrounded excentrically by a dense area of fibrous tissue.

38 *mm.*—A fibrous area surrounding a small artery and vein is seen at this point.

45·5 *mm.*—An oval area, 1 × ·25 mm. in diameter, of concentrically arranged nucleated fibrous tissue, enclosing a few undoubted degenerate cancerous cells. This is the focus of fascial cancer nearest to the primary growth.

45·5 *to* 63·5 *mm.*—No recognisable foci of cancer.

From 63·5 mm. fascial foci are seen at the following points :—

63·5 *mm.*—A lymphatic about 100μ in diameter, lying near a small artery. It is filled by vigorous cancer cells, which at one point have ruptured its wall, and are commencing to invade the surrounding tissue. There are but few leucocytes in the neighbourhood. In another section of this series the

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lymphatic is replaced by two smaller ones, and has evidently bifurcated.

72·5 *mm.*—Close to a small vein is a group of about 20 cancer cells. Some of them are degenerate and are apparently being destroyed by the fibrous tissue which surrounds them.

Zone of Fascial Permeation.

76 *mm.*—A lymphatic full of vigorous cancer cells in the deep subcutaneous tissue. It is 160μ in diameter, and is lined by endothelium. No leucocytic reaction.

77 *mm.*—A cylindrical mass of vigorous cancer cells, 100μ in its short diameter, and 800μ long, lying in a space lined by endothelium. No sign of inflammatory reaction round the space. It is evidently a lymphatic in longitudinal section, since normal blood-vessels can be seen quite close to it.

78 *mm.*, 79 *mm.*, 81 *mm.*, 83 *mm.*—At each of these points a narrow permeated lymphatic, filled but not distended by cancer cells, is seen either in transverse or longitudinal section. The carcinomatous epithelium exhibits no signs of degeneration. (Fig. 2 represents this region.)

83 *to* 90 *mm.*—Fascia free from cancerous invasion.

Muscle.—Along this strip the muscle appears to have entirely escaped invasion.

SUMMARY OF HISTOLOGICAL EXAMINATION, STRIP A.

From the edge of the ulcerated growth down the right arm cancer had extended microscopically in the deep fascia for 83 mm., and in the skin for 84 mm. Beyond this point the tissues showed no cancer, and especially no isolated foci such as might result from embolism.

The invaded length of deep fascia is clearly divisible into two zones:—

(a) The peripheral zone, which forms a narrow microscopic growing edge about 7 mm. wide, in which the fascial lymphatics are full of vigorous cancer cells, and are not yet ruptured, nor even much distended, by the growth within them. (Fig. 2 represents this zone.)

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(b) The proximal zone, about 76 mm. wide, in which a process of perilymphatic fibrosis is going on, which ends in the destruction of the permeated fascial lymphatics, and their replacement by solid threads of fibrous tissue. This process can be seen half completed in the focus at level 45·5 mm., where the appearances are similar to those shown in Fig. 9. For the most part, however, fibrosis has proceeded so far that the deep fascia shows cancer foci only at very few points. The fibrous areas free from cancer round several of the blood vessels towards the proximal end of the strip undoubtedly represent the termination of the process of perilymphatic fibrosis.

Opposite to the microscopic growing edge of the cancer—*i.e.*, in the zone of permeation—the skin showed merely two very minute nodules. These nodules were isolated from each other. A permeated lymphatic was traced obliquely in a distal direction from the deep fascia of the *proximal* zone towards one of these nodules (see Fig. 2). They were not apparently connected with the distal zone of permeation, but simply overlapped it. It is therefore probable that the invasion of the skin was consequent on invasion of the deep fascia, not *vice versâ*. This question will be discussed later.

Strip B.—Extending for 83 mm. from the Lower and Outer Edge of the Ulcerated Mass of Growth Downwards and Backwards across the Lower Ribs and Lumbar Fascia.

The strip was divided into seven blocks, the majority of which were cut in serial section, so that not only was the strip examined in its whole length, but for an appreciable portion of its width. In all about 200 sections from it were examined.

In the description which follows the figures refer to the distances from the ulcerated edge of the growth.

Skin.—The naked-eye and microscopic appearances of the skin were identical with those seen in Strip A. The skin is invaded for 49 mm., *i.e.* for exactly the same distance as the deep fascia. Between the closely set subcutaneous nodules,

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whose size varied inversely as their nearness to the primary growth, the skin showed interstitial or lymphatic growth to a greater or less extent. From 36 mm. to 49 mm., however, there is no continuity in the cutaneous foci. In this stretch of tissue only two minute skin nodules are visible, with permeated lymphatics near them. Moreover these nodules are not present in all the sections.

The invasion of the skin in the distal portion of the strip has therefore a discontinuous character, while, on the other hand, invasion of the fascial plexus in the distal portion of the strip is emphatically by continuous growth. In Case II. therefore, though less decisively than in Case I., the evidence points to the spread of cancer, not along the skin, but along the deep fascia with secondary vertical efflorescences towards the other layers.

Subcutaneous Tissues.—A few nodules are present here and there in the subcutaneous fat. An occasional permeated lymphatic can be seen. Sometimes the "tail" of a skin nodule is continued down into the deep tissues by such a permeated lymphatic.

Deep Fascia.—The deep fascia is invaded by the centrifugal growth of cancer along its lymphatic plexus. The invaded area is divisible into two zones, a peripheral one of lymphatic permeation and a proximal one where the permeated lymphatics are partially or completely destroyed by perilymphatic fibrosis.

In this strip two strong fascial layers, separated by a thin layer of fat, were present over the muscles. Most of the permeated lymphatics lay in the more superficial of these layers.

Zone of Nodules, permeated Lymphatics partially or completely Fibrosed.

0–7 *mm.*—Deep fascia missing from the strip.

9 *mm.*—A circular mass of nucleated fibrous tissue, enclosing in its meshes a few degenerate cancer cells, and surrounding what appears to be a ruptured lymphatic containing similar cancer cells. This fibrous area lies at the point of junction of a fibrous septum with the deep fascia. Above,

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the fibrous septum runs into the "tail" of a subcutaneous cancer nodule (Figs. 12, 13, & 14).

10 *mm.*—A similar fibrous area, about 600μ in diameter, enclosing a large number of degenerate cancer cells (Fig 10). At the other end of the series of sections taken from this particular block, this area is almost entirely fibrous, and contains only one or two cancer cells (Fig. 11). Its diameter has decreased to 300μ.

14–19 *mm.*—Deep fascia missing from the section.

25 *mm.*—In the deep subcutaneous tissue, lying close to a large artery, are two minute lymphatics containing a few degenerate cancer cells. Just superficial to these is another permeated lymphatic, in which the central cells are swollen and degenerate, while the layer of cells touching the endothelium stains well. There is interstitial invasion of a well-defined area of fibrous tissue which surrounds the lymphatic, but at this level no rupture can be seen in the wall of the vessel. Still nearer the skin is a subcutaneous nodule 1 mm. in diameter not reaching up to the dermis.

28 *mm.*—A lymphatic about 160μ in diameter containing degenerate cancer cells. Close to it is a group of cancer cells lying interstitially, which have apparently escaped through a rupture in the wall. There are a few leucocytes near the cancer focus.

29 *mm.*—A space 500μ in diameter, lined by endothelium. It is filled by degenerate cancer cells, and is probably a distended but still unruptured lymphatic.

31 *mm.*—A similar lymphatic in oval section, 500 by 100μ.

35 *mm.*—A distended permeated lymphatic, 600 by 150μ. At one point the wall has given way and the cancer cells are beginning to pass into the tissues. At this point the mass of cancer cells is being invaded by leucocytes.

Zone of Permeation.

35·5 *mm.*—A small cancerous lymphatic 150μ in diameter.

38 *mm.*—A space 600 by 200μ, filled by degenerate cancer cells and lined, at any rate partially, by endothelium. At this

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level a permeated lymphatic can be traced in longitudinal section for some distance into the muscle.

39 *mm.*—A group of cancer cells, measuring about 500μ in diameter, showing marked leucocytic invasion and fibrosis. Some of the cancer cells still look vigorous.

43·5 *mm.*—Throughout a series of sections there is a focus of cancer at this level. Its character, however, varies considerably. In some sections one or more cylinders of cancer cells are seen, measuring about 35μ in their short diameter. These are evidently lymphatics filled but not distended by cancer cells. In other sections an oval area of cancer cells about 200μ in diameter is visible, with a narrow permeated lymphatic running out of it.

49 *mm.*—In some of the sections, but not in all, narrow lymphatics, filled but not distended by cancer cells, are seen at this level. In other sections again, an oval area of cancer cells 150μ in its short diameter is present at the same level. Possibly these expansions represent the nodal points of the fascial plexus.

49 *mm. to* 83 *mm.*—Tissues free from cancer along their whole length. In order to examine the breadth as well as the length of the strip, a series of sections taken from the block just beyond the microscopically determined growing edge was carefully examined. No cancer was found in any section of the series, while it was present in every one of the sections taken from the preceding block.

Muscle.—The muscle seems to have escaped invasion entirely, except at one point. About 38 mm. from the proximal end of the strip, in some of the sections, a small permeated lymphatic can be traced for a long distance down into the substance of the muscle. The point where this lymphatic was found must have been in the lumbar region, just below the 12th rib. Since the parietes are very thin, cancer might thus invade the perinephric fat and reach the lumbar glands.

Among 329 autopsies on breast cancer at The Middlesex Hospital during the last thirty years, I found six in which the kidneys, suprarenal capsules, or lumbar glands were invaded without other abdominal metastases, and without thoracic metastases. In three of these cases subcutaneous nodules, an

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index of wide parietal dissemination, were present. Subcutaneous nodules were found in only 22 per cent. of the whole number of cases. These statistical facts lend an interest to the preceding observations.

COMPARISON OF STRIPS A AND B.

The absolute distance of the microscopic edge of the growth from the margin of the ulcer was in the case of Strip A, 84 mm.; in the case of Strip B, 49 mm. On the centrifugal hypothesis these distances should be approximately equal if measured from the actual point of origin of the growth, but this precise point could not be determined. The area of centrifugal spread is of course not a mathematical circle.

Microscopically the appearances indicated that permeation was extending rather more rapidly down the arm than into the loin. But the appearances in the two strips were in all important respects identical. The qualitative identity of two radial sections extending from the growth in widely divergent directions, chosen at random, amounted to an almost complete proof of the centrifugal hypothesis for this particular case.

COMPARISON OF CASE II. WITH CASE I.

This case differs from the preceding one in several important respects, while it nevertheless shows the same processes at work. In Case II. the proliferation of the cancer cells was evidently less rapid, and the inflammatory reaction was more successful in checking and limiting dissemination.

The zones traceable round the primary growth are the same as in the previous case, but they are not so well defined. The zone of permeation, though well marked in both strips, is a very narrow one, and consequently the cutaneous efflorescences belonging to the zone of fibrosis actually overlap it in some sections. On the other hand the zone of partial perilymphatic fibrosis is a very wide one, and is not clearly marked off from the zone of nodules with completely fibrosed lymphatics. The latter corresponds to the peripheral part of the large cancerous ulcer, and to the proximal portions of the strips examined. In the case of Strip A only a single obsolescent focus of cancer was present on the deep fascia in

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the first 63 mm. of its length. Only two similar foci were present in the first 28 mm. of the length of Strip B.

The destruction of the permeated fascial lymphatics is better seen than in Case I., because it was not obscured by rapid and extensive formation of nodules in the adjoining layers.

But the main importance of the case lies in the fact that it demonstrates the various stages of perilymphatic fibrosis at different points along the length of the same lymphatic (Figs. 10 and 11).

CASE III.

A recurrent ulcerating scirrhus of the right breast, with metastases in the thorax and abdomen. A nearly vertical strip of tissue extending downwards from the ulcer was examined by means of horizontal sections taken at intervals along its length. Unfortunately it did not in its whole length include all the layers of the parietes. Subcutaneous nodules were present, the lowest of which was situated eight inches above the umbilicus. A section of the skin half an inch above this nodule, between it and the primary growth, was absolutely free from cancer; there was, therefore, no continuity of infection along the skin. The dermis around the nodule was only infiltrated for a very short distance.

Two and three-quarter inches below this nodule the small lymphatics lying upon or in the anterior layer of the Rectus sheath were found blocked by lines of cancer cells, while the subcutaneous tissue up to the dermis was quite free from growth. Sections, three in number, taken at intervals above this point, showed more advanced infection of the deep fascia, as the primary growth was approached.

Seven sections taken at intervals below the lowest point where the deep fascia was found infected, showed that the tissues beyond this point were entirely free from growth, at any rate down to one inch below the umbilicus.

The histological examination in this case, imperfect though it was, showed that invasion of the deep fascia extends a long way beyond the remotest subcutaneous nodule. It proved that healthy skin may intervene between adjacent cutaneous

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metastases, and suggested that the cancerous process in the deep fascia is one of actual continuous growth along lymphatic vessels. The absence of isolated foci of growth below a definite level above which no section of deep fascia free from growth was found, was much opposed to the embolic view of the spread of cancer in the deep fascia.

This case is inserted because it confirms in some particulars the conclusions arrived at from consideration of Cases I. and II.

CASE IV.

The right breast had been removed for cancer. There was no ulceration of the scar. Subcutaneous nodules were present in large numbers, and were arranged in definite lines radiating from the right axilla. They did not cross the middle line except on the abdomen, where a few small ones could be felt in the left hypochondriac region. One definite line ran directly upwards across the junction of the middle and outer thirds of the clavicle, and was continued in the posterior triangle of the neck. A second ran horizontally outwards across the deltoid muscle. Four lines of nodules, diverging somewhat as they descended, ran downwards from the axilla over the lateral aspect of the thorax. One of these lines descended direct to the inguinal glands; it was formed of half a dozen large nodules in the thoracic region, of a single large one about the level of the umbilicus, and of a tiny *fascial* nodule, not involving the skin, about three inches above Poupart's ligament. There were nodules also in both scapular regions and in the loins. A nodule of growth was found in the left breast, and in each of the lateral lobes of the thyroid. The axillary, supraclavicular and inguinal glands on both sides were cancerous. The left clavicle was fractured. Visceral metastases were present in the chest.

The histological examination of the case was imperfect. Permeated lymphatics were found upon and in the deep fascia one inch above Poupart's ligament. Near this point a vertical cord of growth, evidently a permeated trunk lymphatic, was visible, running downwards to the inguinal glands. An inch higher up the tissues were invaded up to the dermis. Several

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permeated lymphatics were also detected in sections taken three inches above the costal margin, just to the right of the middle line.

A section of a muscular nodule to the right of the middle line just below the costal margin, showed cancer cells lying between the fibrous bundles of the Rectus sheath, but no permeated lymphatics were seen either in this situation or (*a*) an inch above the xiphoid cartilage just to the right of the middle line; (*b*) an inch below the xiphoid cartilage; (*c*) two inches below the umbilicus.

In this case the process of centrifugal spread seems to have recommenced from a focus of growth in the right axilla left behind at the time of the operation.

The scarred area left by the operation seems to have hindered the extension of nodules to the left side of the body, but, nevertheless, the case illustrates their centrifugal spread.

Fascial permeation is here seen extending beyond the remotest visible subcutaneous nodule, and at a great distance from the original focus of growth.

The case, though imperfectly examined, is inserted to show how widely permeation may extend. In Case I. the process of permeation, though it had extended downwards over the abdominal wall, had not crossed the water-parting which separates the lymphatic area of the axillary glands from that of the inguinal glands. This water-parting or neutral zone between the contiguous lymphatic areas corresponds to a horizontal line running through the umbilicus. It is a region of fine anastomoses, nowhere traversed by trunk lymphatics, admirably adapted to filter off any cancer cells which attempt to reach the inguinal glands by a reflux lymph stream. The present case shows that permeation is capable of penetrating through this neutral zone into adjoining lymphatic areas. This appears to be the essential event of dissemination.

The freedom of the deep fascia from permeation at points near the growth, and its presence at points further removed from it, are explained by Cases I. and II., which show that fibrosis follows permeation, and that the growing edge may advance as a ring, within whose inner margin the evidence of permeation has vanished.

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CASE V.

The patient first began to ail nine or ten months before death. Six months before death a lump was felt in the left breast. Jaundice supervened six weeks before death. At this time large glands were present in both groins and in both axillæ, along with very numerous nodules in the subcutaneous tissue. The largest nodules were near the breast, and at the back of the neck, and many of these were adherent to the skin. Diminishing in size and losing their adhesion to the skin, they reached over the abdomen nearly down to the groins, but there were no nodules on the lower limbs. Very tiny fascial nodules could be felt in the left arm down to the elbow, along the line of the axillary vessels, and half way down the right upper arm. Fairly large nodules were present on the neck, a few on the scalp, and on the side of the face.

The subcutaneous tissue of the left arm conveyed to the examining hand a markedly different sensation above and below the elbow. On the upper arm the tissues felt distinctly granular apart from the separately palpable nodules, while below the elbow the tissues were perfectly smooth, soft, and normal.

At the autopsy a still more extensive distribution of nodules was found. They were universally, though irregularly, distributed over the body, except on the distal portions of the limbs. The remotest nodules, minute shotty lumps on the deep fascia, were situated as follows:—

On the summit of the scalp, 18 in. from the primary growth.

On the left arm, 1 in. above the elbow, 11 in. from the primary growth.

* On the right arm, 1 in. below the elbow, 19 in. from the primary growth.

* On the left thigh, 6 in below the anterior superior spine, 18 in. from the primary growth.

* On the right thigh, 7 in. below the anterior superior spine, 21 in. from the primary growth.

The lowest nodule on the back was situated over the 2nd sacral spine, 15½ in. from the primary growth.

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There was a nodule above the right posterior superior spine, 17 in. from the primary growth.

There was a nodule above the right iliac crest, 15½ in. from the primary growth (measured round the right side of the body).

In the situations marked with an asterisk (*) nodules certainly became recognisable only during the last fortnight of life. The largest nodules were situated at the back of the neck, in the scapular regions, over the front of the chest, and over the left clavicle. Upon the abdomen they were small and thinly scattered.

There were in this case numerous visceral metastases, the distribution of which does not concern us. Microscopically the growth was diagnosed as an endothelioma, a type of neoplasm particularly likely to show lymphatic spread, in consequence of its genetic relations with lymphatic channels. Its cells were of moderate and uniform size, with round vesicular nuclei. When aggregated together in alveoli, many of the central cells showed marked vacuolation. In places complete disintegration of the central cells had occurred, and nothing but a granular débris remained.

On the clinical and macroscopic side the case showed conclusive evidence of rapid centrifugal dissemination. A fortnight before death, for instance, no nodules were found on the thighs, while at the autopsy nodules were present as far down as 6 in. below the anterior superior iliac spines. The same phenomenon was witnessed in the right arm, while the distal portions, both of the upper and lower limbs, remained entirely free from nodules, and perfectly smooth to palpation.

The nodules present in this case did not belong to the ordinary type of subcutaneous nodules. A few were situated in the subcutaneous tissue, but most of them lay either on the deep fascia or in the superficial layer of the muscles. It should also be noted that the largest nodules were in the immediate neighbourhood of the growth, and that only these were adherent to the skin. So that nodules presumably made their earliest appearance close to the primary growth. The distribution of the nodules in this case strongly indicates that fascial and muscular nodules obey the same centrifugal law

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which, in a previous paper, has been shown to apply to true subcutaneous nodules and to bone metastases.

In order to obtain microscopic evidence for or against the hypothesis put forward above, the following strips of the parietal tissues were removed and examined histologically along their whole length :—

(1) A strip of tissue commencing above at the right acromial process, and passing down the outer side of the arm to a point 6 in. above the wrist.

(2) A coronal strip of the scalp from the vertex to the ear.

(3) A median strip extending on the front of the body from the chin down to the pubes.

The results of the microscopic examination were in this case negative. Numerous isolated nodules were found on the one hand in the subcutaneous tissue, and on the other hand in the muscle. The skin had almost everywhere escaped invasion. No sign of invasion of blood vessels was seen. It could be made out with great probability that the muscles were first invaded on their superficial aspect, for the two youngest isolated foci of cancer seen in the muscle were just beneath the overlying fascia.

At one point a tiny isolated group of cancer cells in the subcutaneous tissue was surrounded by leucocytes. The cancer cells were degenerate, but still clearly recognisable, and the view suggested itself that this focus was being destroyed by phagocytosis.

Having described the five cases in detail, I now propose to give a general account of the processes of permeation, perilymphatic fibrosis, and nodule formation, which appear to be the essential factors in the parietal dissemination of breast cancer. This account is based on the cases I have related.

PERMEATION AND ITS SEQUELS.

The growth of cancer along the lymphatic vessels is, no doubt, simply the result of that same tendency to take the direction of least resistance, which on the surface of the body manifests itself in fungation. By preference the process seems to follow vessels of not less than 40 or 50μ in diameter, avoiding for a time those of smaller calibre, and, therefore,

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higher resistance (see Fig. 4). For this reason the parietal growing edge of a breast cancer follows the plane of the deep fascia where the main lymphatic plexus is situated.

The trunk lymphatics also escape permeation, but for a different reason. In them the lymph stream is strong enough to sweep away as emboli any cancer cells gaining an entrance, until in a late stage their outlet is dammed by growth in the glands, or by external pressure on their walls. This is a sufficient reason for the rarity with which cancer is found in the thoracic duct. Nevertheless, when cancer of the thoracic duct is met with, the duct and its tributaries are often so obviously converted into solid cancerous cords* that the process of permeation can be seen with the naked eye.

For the naked-eye recognition of lymphatic permeation, however, vessels of large size are not absolutely necessary. In favourable situations the process can be seen even in very minute lymphatic vessels.

Cancer cells which escape into the pleural cavity are apt to implant themselves at some point on its surface, and originate pseudo-papillomatous secondary growths. Round such an implantation growth, a roughly circular, opaque, and slightly thickened area of pleura can often be seen, perhaps an inch or two in diameter. Close observation reveals this opaque area as a network of fine white lines, just visible to the unaided sight. The microscope shows these lines to be vessels of the sub-pleural lymphatic plexus filled by cancer cells.

The small implantation growth and the permeated circle of pleura round it may be regarded as a rough model on a small scale of a primary mammary growth and of the surrounding invaded area of the parietal lymphatic plexus.

In certain situations, under the misleading name of *lymphangitis carcinomatosa*, permeation has long been recognised and described. Borst† describes the process in the following terms:—

"A very interesting form of lymph-vessel metastasis is the so-called *lymphangitis carcinomatosa*. One meets with

* See Hillier, "Carcinoma of the Thoracic Duct," Trans. Path. Soc., 1903, p. 153.

† Borst, "Die Lehre von den Geschwülsten," Wiesbaden, 1902, vol. ii., p. 712.

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it in the serous membranes, in the diaphragm, in the lungs, and in the liver. All the lymph vessels of the affected region are filled with cancer masses, so that the microscopical appearances not only resemble, but even surpass an artificial injection of the lymphatic plexus."

It will be seen that Borst regards this process as peculiar to certain organs—that he does not recognise it, for instance, as occurring in the parietal lymphatics, nor describe it as taking any important share in dissemination. It will, I think, ultimately be found that permeation invariably occurs in the lymphatics round all carcinomata which give rise to metastases. It must, however, be admitted that in certain cases, such as Case V., permeation cannot be demonstrated anywhere in the tissues. But a lymphatic along which cancer cells have pushed their way does not persist unchanged, either usually or necessarily, until the patient's death affords an opportunity of observing it. It is in accordance with our knowledge of the reaction of the tissues to other foreign bodies that a process of fibrosis should occur round the permeated lymphatic and should usually succeed in destroying the slender cylinder of cancer cells within.

Indications of the nature of this process have already been given, but it must now be studied more in detail. For convenience of reference I have called the process "perilymphatic fibrosis."

Perilymphatic fibrosis.—M. B. Schmidt has shown that in a blood vessel cancer cells excite an organizing thrombosis which usually ends in their destruction. So far as I have seen, the lymph exhibits no such thrombotic reaction to cancerous invasion. Nor, in the tissues around a permeated lymphatic, is there at first any sign of inflammatory reaction.

Soon, however, the elastic tube in which the cancer cells lie is stretched by their proliferation to several times its normal diameter, and there ensues a process of inflammatory fibrosis around the vessel, analogous to that which on a large scale follows the prolonged distension of a hollow viscus such as the gall-bladder. The commencement of this process is heralded by the appearance of small round cells in the perilymphatic tissues.

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In the course of time the hyper-distended lymphatic bursts, and slight traumatic hæmorrhage often occurs in consequence around the enclosed group of cancer cells. The cylinder of cancerous epithelium thus released from pressure is now apparently free to invade the adjoining tissues. But the inflammatory reaction already present is greatly intensified by the rupture of the lymphatic. Abundant round-celled exudation takes place. Soon granulation tissue takes the place of round cells, and forms a definite new capsule for the cancer cells. The further organisation of this granulation tissue into fibrous tissue is accompanied by shrinkage of the fibrous capsule, which contracts upon and slowly strangles the remaining cancer cells. Ultimately the original permeated lymphatic is replaced by a slender cord of fibrous tissue in which no cancer cells can be seen.

That the rupture of a permeated lymphatic does not invariably lead to local invasion of the surrounding tissues, depends also upon the point that the cancer cells set free are often incapable of growth. The proliferating cancer cells within a lymphatic are themselves subject to the same harmful pressure which they exert upon its walls. The effects of this pressure are often to be seen in their swollen, degenerate, and unstained character. Frequently only the layer of cells abutting immediately on the endothelium preserves the appearances of vitality. So that when the cancer cells rupture the lymphatic and are free to invade the tissues, they are neither numerous enough nor sufficiently vigorous to withstand the traumatic inflammatory reaction which follows.

As a curative process perilymphatic fibrosis has unfortunately certain defects. In the first place it does not follow permeation with sufficient promptness to overtake the microscopic growing edge where permeation is just beginning.* In the second place, the contraction of the perilymphatic fibrous tissue helps to force cancer cells along the smaller tributary lymphatics, which on account of their higher resistance have hitherto escaped invasion. Passing along these vessels the cancer cells reach and permeate the bundle of lymphatic capillaries from which each of the small

*Cf. Lazarus-Barlow, "Textbook of General or Experimental Pathology," 2nd Edition, p. 515.

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lymphatic vessels arises. The wall of these lymphatic capillaries consists merely of endothelium, and is quite unfitted to resist a pressure such as growing cancer cells can exert. Before an adequate inflammatory reaction can ensue the cancer cells rupture the lymphatic capillaries and invade the surrounding tissues. If, therefore, living cancer cells in this way reach the extreme periphery of the lymphatic system, they are able to originate metastases. Such metastases are often sharply circumscribed nodules, a form which may be determined, according to my observations, by extension of cancerous growth along all the lymphatic capillaries which drain into some one lymphatic. In its early stages the nodule maps out the limits of this capillary lymphatic area.

The metastases which thus arise in the various layers of the parietes, though apparently discrete and sporadic, are genetically continuous with the primary growth. But perilymphatic fibrosis has destroyed the evidence of their continuity with it.

It should be especially noted that in their earliest stages the processes I have described are only to be seen at the microscopic growing edge, and that as one passes towards the primary growth they become visible in more and more advanced stages. Thus, as might be expected, all these stages may be recognised in a single favourable radial section of the primary growth extending to its microscopic growing edge. To trace the course of events along the length of a single lymphatic is naturally most difficult. But Figs. 11 and 12, showing the middle and the penultimate stages of fibrosis, are derived from a fortunate series of sections of the same lymphatic at different points along its length.

THE ZONAL ARRANGEMENT OF BREAST CANCER IN THE PARIETES.

It will be seen that the parietal metastases, except the embolic ones, which probably occur only in the lymphatic glands, are really parts of the primary growth. The expression "primary growth" may, however, be defined as the region of interstitial infiltration round the original primary

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focus. As thus defined the primary growth is surrounded by three zones :—

(1) The zone of isolated or confluent nodules in which the permeated lymphatics have been destroyed.

(2) The zone in which perilymphatic fibrosis is actively progressing, and in which nodule-formation on either side of the main lymphatic plexus is seen in an early stage.

(3) The zone of fascial permeation. This is subdivisible into a proximal zone characterised by distension and rupture of the lymphatics, and by perilymphatic leucocytosis, and a peripheral zone in which distension of the lymphatics has hardly commenced, and in which therefore no inflammatory reaction has yet taken place.

Even the negative results of Case V., which cannot in any case outweigh the positive evidence of Cases I. to IV., are best explained by the theory of permeation. I am not aware of any theory but that of permeation which will explain the centrifugal extension so clearly manifested in this case by the clinical evidence. And as regards the microscopical evidence it is at least possible that the strips examined, long though they were, failed to pass beyond the zone of isolated nodules into the outlying zones of active fibrosis and of permeation.

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DESCRIPTION OF FIGURES (Plates I.–VII.).

FIG. 1, from Case I. shows the parietal edge of a breast-cancer of moderately rapid growth. It is a nearly median section of the parietes in the sagittal plane, taken from the epigastric region of the abdomen just below the ensiform cartilage. On the left is seen the skin surface, and to the extreme right a superficial layer of the Rectus muscle. Immediately overlying the Rectus muscle is the anterior layer of its sheath. In the whole length of the drawing the foci of growth are confined to the surface of the Rectus sheath and to the deeper layer of the subcutaneous tissue. Opposite each focus of growth, along the left of the figure, is a numeral indicating its level in mm. above the umbilicus, and referring to the detailed description of Case I. The skin and muscle are entirely free from growth, though in the region above the figure, *i.e.*, nearer to the primary growth, nodules were found in both these layers.

The figure shows the whole width of the "zone of fascial permeation."

FIG. 2 (× 25), from Case II. Strip A, shows the parietal edge of a breast-cancer of slow growth. Above is seen the skin surface, while at the lower edge is a layer of muscle.

In the fascial layer, along the line A B C, a number of lymphatics are seen in longitudinal section. They are permeated, but not distended, by cancer cells. Fig. 5 shows one of these lymphatics highly magnified. At the point C is the actual growing edge of the cancer in the fascia. In this particular section the skin is invaded about ·3 mm. beyond the fascia. The remotest subcutaneous nodule is seen at G. This nodule is connected with a proximal point in the deep fascia by a fibrous septum D E F, which runs very obliquely in a distal direction. The figure shows the distal part of the "zone of fascial permeation."

FIGS. 3 TO 11.—THE VARIOUS STAGES OF PERMEATION AND OF PERILYMPHATIC FIBROSIS.

Zone of Permeation without Inflammatory Reaction.

FIG. 3 (× 90).—From the abdominal wall, 160 mm. above the umbilicus, at the extreme growing edge in Case I. (see Fig. 1). Crossing the lower half of the field is the anterior layer of the Rectus sheath. Upon its superficial aspect are seen in transverse section two lymphatics filled by cancer cells. Between them is a normal blood vessel. Note the absence of perilymphatic leucocytosis.

FIG. 4 (× 60).—A similar section taken from Fig. 1. A permeated lymphatic is seen in transverse section. Running from it through the anterior layer of the Rectus sheath, and bifurcating on its deep aspect, is a small branch lymphatic, along which permeation has not yet extended.

[To illustrate the proposition that permeation follows the line of least resistance, avoiding for a time the smaller lymphatics. Hence the growing edge of a breast cancer is situated in the deep fascia, in the plane of the principal parietal lymphatic plexus.]

FIG. 5 (× 120).—A highly magnified portion of Fig. 2, from the growing edge in Case II., Strip A. The figure shows a permeated lymphatic in longitudinal section. The lymphatic endothelium is clearly visible. Above and below the

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lymphatic are seen normal blood vessels, also cut longitudinally. The lower one is bifurcating.

[This figure shows that the groups of cancer cells seen in Figs. 3 and 4 are sections of cylinders, not isolated clumps of cells.]

Zone of Permeation with Perilymphatic Leucocytosis.

FIG. 6 (× 96).—A highly magnified portion of Fig. 1. The anterior layer of the Rectus sheath crosses the lower half of the field. The permeated lymphatic visible is beginning to be distended from proliferation of the cancer cells within it. A few emigrated leucocytes are present near an adjacent normal blood vessel. The cancer cells have not yet suffered any injury from the increased intra-lymphatic pressure.

FIG. 7 (× 100).—From Case I. A transversely-cut permeated lymphatic greatly distended by the proliferation of the cancer cells within it. The nuclei of the lymphatic endothelium are consequently only seen at wide intervals. The cancer cells, except the layer next the endothelium, have suffered from pressure, and are swollen, hyaline, degenerate and polygonal. There is moderate perilymphatic leucocytosis.

FIG. 8 (× 72).—From the muscular layer in Case I. The limit of the resistance to distension offered by the wall of the lymphatic has been reached, and the tube has split along one side, but not before, as a result of the increased intra-lymphatic pressure, cancer cells have grown along the small branch lymphatics seen in the upper part of the figure. The rupture of the lymphatic has caused slight hæmorrhage and has much increased the pre-existing leucocytosis. Clearly, therefore, the rupture was an ante-mortem event. This is further shown by the degenerative changes which the extravasated red corpuscles have undergone.

(In Fig. 1 at levels 182·9, 184·5, 186, and 188·3 mm., rupture of lymphatics is also traceable, but in a less recent and unequivocal form.)

Zone of Active Perilymphatic Fibrosis, with early Nodule Formation.

FIG. 9 (× 100).—From Case I. The degenerate cancer cells set free by rupture of the lymphatic are enveloped in a fibrous area infiltrated by round cells, and appear to be in process of destruction.

(The subsequent stages of fibrosis were obscured in Case I. by the abundant formation of nodules which occurred, but they were traced in Case II. along the length of the same lymphatic.)

FIG. 10 (× 45).—From Case II., Strip B. The mass of degenerate cancer cells set free from the ruptured lymphatic is now enclosed in a definite capsule of newly-formed fibrous tissue, in which many leucocytes are still visible. Normal blood vessels are seen at the edge of the field.

FIG. 11 (× 180).—The penultimate stage of perilymphatic fibrosis. A section at another part of its course of the fibrosed lymphatic seen in Fig. 10. To show the characters of the newly-formed fibrous tissue Fig. 11 is much more highly magnified than Fig. 10.

The fibrosed lymphatic has shrunk to about half its diameter. A few cancer cells in the last stages of destruction still persist as islets in the contracting fibrous tissue. Round cells have given place to the fusiform cells of young fibrous tissue, and newly formed capillaries are visible here and there in the fibrous area.

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The Formation of Subcutaneous Nodules.

FIG. 12 (× 20).—From the proximal portion of Strip B, Case II. Above is seen the deepest layer of the dermis, densely infiltrated by cancer, while close to the lower margin of the field, above and to the left of a normal blood-vessel, is a fibrosed lymphatic lying upon the fascial layer which here crosses the figure transversely. The deep fascia in this region is for the most part free from cancer and only here and there still shows obsolescent foci of cancer like the one represented.

The two conical sub-dermal areas of cancerous infiltration are formed by the extension of permeation along the bundle of small lymphatics which by their union form a vertical tributary of the fascial plexus. From the area on the right of the figure a distinct "tail," consisting of a permeated vertical tributary not yet fibrosed along its whole length can be followed for some distance towards the fascia.

FIG. 13 (× 120).—A high power photograph of the "tail" just referred to. It shows a partially fibrosed permeated lymphatic.

FIG. 14 (× 60).—A high-power photograph of the fibrosed lymphatic seen on the fascia in Fig. 12. Cf. Fig. 11.

The Formation of Nodules in Muscle.

The stage preceding nodule formation can be studied in Fig. 8, where cancer cells are extending along the small tributaries of a permeated and ruptured muscular lymphatic.

FIG. 15 (× 100) shows permeation extending to the extreme periphery of the lymphatic system. The lymphatics of origin among the muscular bundles are mapped out as an arborescent figure, with a main horizontally-running branch and vertical side branches. The muscle fibres are still normal, and the permeated lymphatics are not fibrosed.

FIG. 16 (× 150).—The next stage in the formation of muscular nodules. The cancer cells are invading and have partially replaced the muscle fibres themselves, while the permeated lymphatics are undergoing fibrosis, and will ultimately form part of the stroma. A partially fibrosed lymphatic runs horizontally across the centre of the field.

FIG. 17 (× 20).—Below and to the right is seen the edge of a fully formed muscular nodule which appears darker than the normal muscle occupying the greater portion of the field. Crossing the upper part of the field, nearly horizontally, is the plane of separation between muscle and deep fascia. On the extreme right of the field, close to its upper margin, is a permeated fascial lymphatic undergoing fibrosis. Running vertically down to the cancer nodule from the deep fascia in the vertical plane which bisects the field is a fibrous septum containing a permeated and ruptured lymphatic. The cancer nodule was apparently formed by the extension of permeation into the "catchment area" of this lymphatic.

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A CONTRIBUTION TO THE STUDY OF GIANT CELLS IN SARCOMATA.

By W. GORDON TAYLOR, M.A., M.B., B.Sc.

THERE apparently still exists a diversity of opinion upon the question of the occurrence of metastases in connection with the giant cells in myeloid sarcoma; a note upon a case of this form of sarcoma, therefore, is perhaps of value.

Patient, Female, aged 22, admitted for sarcoma of the lower end of the femur. The growth was the size of a cocoa-nut, and projected more from one side of the bone, but it was uncertain whether the growth was endosteal or periosteal. Amputation through the middle of the femur. Death occurred 18 months after the operation, and post-mortem, metastatic deposits were found in the lungs.

On microscopic examination sections of the primary tumour were found to show spindle cells and two or three definite giant cells.

The secondary deposits were largely composed of spindle cells, but also contained a fair number of definite giant cells, easily traceable through a series of sections, and measuring upwards of 40μ in thickness.

The above case is therefore of value in two ways: firstly, it proves clearly that giant-cell sarcomata do form metastases; and secondly, that giant cells are reproduced in the secondary deposits.

On this latter point, the literature is not very definite; many authors, including Borst, make no mention of the occurrence of giant cells in such metastases; others agree that secondary tumours "may arise having the characters of the primary growth"; while Sims Woodhead states that "such secondary tumours as have been examined when found in the position ordinarily affected (the lung), have contained *no* giant cells, but have been simply small spindle-celled sarcomas."

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In the specimen referred to above, the giant-cells were not reproduced in the lung in any abundance, but sections measuring about 12mm. × 6mm. invariably contained one, and often several such cells.

It would therefore appear that giant-cell sarcoma conforms to the general principle that tumours breed true, and that the secondary growths reproduce in every detail the structure of the primary neoplasm,—a belief which the silence of most authors upon the point perhaps tacitly implies. Further it would seem that the giant-cells are not mere accidental inclusions, but an integral part of the tumour.

A somewhat similar case was recorded as long ago as 1858,* in which after removal of a myeloid sarcoma of the upper extremity of the humerus and glenoid cavity of the scapula the growth recurred locally and secondary deposits formed in the lungs. In this case, the external portion of the tumour is described as containing a few "myeloid bodies," whilst the internal or soft portion is composed almost entirely of myeloid bodies. The metastases also contained myeloid bodies.

Sections have recently been cut of the primary growth which has been found to contain a large number of giant cells, although the part examined was not "in great part constituted by giant cells."

* * * *

In order to determine the distribution of multinucleated and giant cells in sarcomata, apart from the typical myeloid variety, some 50 tumours occurring at The Middlesex Hospital have been investigated in this connection, and nearly 9,000 sections have been cut and examined. The method of procedure was as follows :—A series of 20 sections, about 8-10μ thick was cut, and then a portion of the stock was cut away ; then another series of about 20 sections was cut and mounted, and so on. The actual number of sections of each tumour varied, but in many cases upwards of 200 sections were examined.

In making this investigation a distinction was made between "multinucleated" and "giant" cells. Cells containing more than one nucleus were not regarded as giant cells unless they

* Trans Path. Soc. Lond., vol. ix., p. 367. The primary growth is preserved in the Museum of The Middlesex Hospital.

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contained more than 4 or 5 nuclei, could be traced through more than one section (*i.e.*, had a thickness greater than 8μ), and had a pronounced affinity for eosin. With regard to the latter point it is my experience from the present investigation that multinucleated cells undoubtedly stain less deeply with eosin than giant cells as above defined.

Definite giant cells were found in 4 periosteal sarcomata (mandible 1, frontal bone 1, tibia 2), and in one sarcoma of the parotid. In no other cases of the series were definite giant cells met with.

The case of sarcoma of the mandible was the only one (apart from the two cases mentioned above) which contained giant cells and formed metastases. These metastases were in the lung, lymphatic glands, and one adrenal, and showed the presence of giant cells.

Multinucleated cells were found in one spindle cell sarcoma of the ovary, one small round cell sarcoma of the stomach, one small round cell sarcoma of the nose, one mixed small and large round cell sarcoma of cervical glands, and (doubtfully) in one large round cell sarcoma of the breast.

In the remaining 41 cases no trace of giant cells or of multinucleated cells was found either in the primary or the secondary growths.

The results of the research may be summarised thus :—

1. Giant cells were found only in sarcomata connected with bone, excepting one case of sarcoma of the parotid.
2. Multinucleated cells, as distinguished from giant cells, were not found in any sarcoma connected with bone.
3. Giant cells were not found in the secondary growths of sarcomata containing giant cells and forming metastases unless the primary growth showed the presence of one or more giant cells in every microscopic section.
4. When the first section examined revealed the absence of giant cells they were very rarely found in subsequent sections.

[TABLE.

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TABLE OF CASES USED IN AN INVESTIGATION ON GIANT CELLS IN SARCOMATA.

No.	Site of Primary Growth.	Histological Characters.	Presence or Absence of Giant or Multinucleated Cells.	Number of Sections Examined.
1	Mandible (α)	Small round	Giant cells	100 + 120*
2	"	Spindle	0	100
3	"	Round	0	200
4	"	Small round	0	50
5	Maxilla	"	0	200
6	"	Spindle	0	150
7	Antrum	Small round	0	50
8	Frontal bone	"	Few giant cells	50
9	Innominate bone	Round	0	200
10	"	"	0	200
11	Femur	"	0	200
12	Tibia	Mixed small round and spindle	Few giant cells	50
13	"	—	0	150
14	"	Round and spindle	Very few giant cells	50
15	Nose	Mixed	0	200
16	"	Small round	Few multinucleated	50
17	Cheek	Large spindle	0	200
18	Pectoralis major	Round	0	200
19	Rectus femoris	"	0	200
20	Gluteus maximus	Spindle	0	200
21	Stomach	"	0	100
22	"	Mixed	0	200
23	"	Small round	Multinucleated cells	50
24	"	"	0	50
25	Rectum	"	0	200
26	Omentum	Spindle	0	200
27	Parotid	Mixed	Few giant cells	100
28	Thyroid	Spindle	0	50
29	"	Mixed	0	50
30	Breast	Large round	Doubtful multinucleated	50
31	"	Haemangiosarcoma	0	200
32	Bladder	Spindle	0	50
33	"	Round	0	200
34	Ovary	Spindle	Multinucleated cells	50
35	"	Mixed	0	200
36	Testicle	Small round	0	600
37	Kidney	Mixed	0	100
38	Uterus	Spindle	0	50
39	Bronchus	Small round	0	50
40	Lung	"	0	200
41	Mediastinal glands	Lymphosarcoma	0	100
42	"	Small round	0	100
43	"	"	0	40
44	"	Lymphosarcoma	0	40
45	Cervical glands	"	0	400
46	"	Mixed small and large round	Multinucleated cells	100
47	Back (β)	Melanotic	0	200 + 100*
48	Vulva	"	0	200
49	Frontal lobe of brain (γ)	"	0	50
50	Skin of thigh (δ)	"	0	250 + 1000*

(α) The following metastasic deposits examined: Lung, lymphatic gland, adrenal.
(β) Metastatic deposit in axillary gland examined.
(γ) No. 49 was secondary to eyelid.
(δ) Metastatic deposits examined in liver, lung, lymphatic glands.
* Primary + metastatic growths.

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CONTRIBUTION TO THE STUDY OF THE BLOOD IN MALIGNANT DISEASE.

II.—THE QUESTION OF THE FORMATION OF SPECIFIC PRECIPITINS. (PRELIMINARY COMMUNICATION.)

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The following observations were made during the course of a research having for its object the determination whether a precipitin reaction specific to cancer can be obtained.

Experiments were first made regarding the effect of heat on the precipitins produced by the intra-peritoneal injection into rabbits of cancerous fluids. These and all other experiments were carried out on the general lines indicated by Nuttall in his work on "Blood Immunity and Blood Relationship," Cambridge, 1904.

Exp. 1.—The antiserum employed was one produced by injecting serum from a case of sarcoma of the jaw (AS2). A short description of the method of producing this antiserum is as follows:—

5—10—10—10—14 . . . serum injected in cc.
4—3—4—5 . . . days between injections.

Portions of the antiserum were kept for half an hour in a water-bath at different temperatures, and then were tested quantitatively by the method of Nuttall and Inchley* against normal human serum (NHS). The quantities of each reagent were as follows:—

·5 cc. AS2 + 1 cc. of 1-21 dilution of NHS.

* Journal of Hygiene, iv., 1904.

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The results were as follows:—

A.	untreated antiserum . . .	·0150 cc. precipitum
B.	antiserum kept at 55° C. . .	·0141 cc. ,,
C.	,, ,, 60° C. . .	·0133 cc. ,,
D.	,, ,, 65° C. . .	·0083 cc. ,,
E.	,, ,, 70° C. . .	trace only

From this it would seem that the precipitating power of the antiserum was diminished by the comparatively low temperature of 55° C., that it underwent further diminution at 60° C., that it became markedly weakened at 65° C., and that it was destroyed at 70° C.

In working with another antiserum produced by injecting serum from a case of squamous cell carcinoma, heating for half an hour at 70° C. was found to cause opalescence and a seeming gelatinizing of the serum. These results are in line with those of other observers (Nuttall, pp. 115–6), except in respect of the weakening of precipitating power at temperatures below 60° C.

It is maintained by some observers (Müller,* Eisenberg,† and von Pirquet‡) that when a precipitating antiserum is inactivated by heat its precipitins are altered, losing their power of precipitating while retaining their power of combining, such bodies being termed "precipitoids." Precipitoids are said to have a greater affinity for precipitable substances than precipitins, and so prevent the action of the latter. Michaelis,§ on the other hand, wholly failed to demonstrate the formation of precipitoids.

It was thought desirable to make some experiments in this direction.

Exp. 2.—The antiserum employed was one produced by injecting serum from a case of spheroidal cell carcinoma (AS7). The method of producing this antiserum was as follows:—

10—10—10—10—10—10 . .	serum injected in cc.
4 — 4 —12— 7 — 5 . .	days between injections.

* Münch. Med. Wochenschr. xlix. pp. 1330–2.
† Centralbl. f. Bakt. xxxi., pp. 773–6.
‡ Ibid. xxxii., pp. 60–74.
§ Centralbl. f. Bakt. xxxii.

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A portion of this antiserum was kept in a water bath for half an hour at 67·5°–68·5° C. (IAS7). There was no opalescence. Normal rabbit serum (NRS) was also used, and normal human serum (NHS). The quantities of each were as follows :—

·2 cc. of AS7 (sometimes + ·2 cc. of IAS7) + 1 cc. of 1–100 dilution of NHS.

In both 2 and 3 (below) the two rabbit sera (AS and IAS) were kept in contact for half an hour before being added to the human serum to ensure thorough mixing.

1. AS7+NHS . . .	·0075 cc.	precipitum
2. AS7+IAS7+NHS . .	·0090 cc.	,,
3. AS7+NRS+NHS . .	·0080 cc.	,,
4. NRS+NHS . . .	trace	,,
5. IAS7+NHS . . .	trace	,,

Exp. 3.—The same antiserum (AS7) was kept at 66·5°–67·5° C. for half an hour. There was no opalescence. The experiment was as before.

1. AS7+NHS . . .	·0080 cc.	precipitum.
2. AS7+IAS7+NHS . .	·0090 cc.	,,
3. AS7+NRS+NHS . .	·0090 cc.	,,
4. NRS+NHS . . .	trace	,,
5. IAS7+NHS . . .	trace	,,

Exp. 4.—The same antiserum (AS7) was heated to 68·5°–69·5° C. for half an hour. There was distinct opalescence. The experiment was as before.

1. AS7+NHS . . .	·0085 cc.	precipitum
2. AS7+IAS7+NHS . .	·0085 cc.	,,
3. AS7+NRS+NHS . .	·0090 cc.	,,
4. NRS+NHS . . .	trace	,,
5. IAS7+NHS . . .	trace	,,

Exp. 5.—An antiserum produced by injecting pericardial fluid from a case of sarcoma of the jaw (AS3) was heated to 67·5°–68·5° C. (IAS3). The antiserum itself was produced as follows :—

5—10—10—20 . .	serum injected in cc.
4 — 3 —12— 8 . .	days between injections.

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The experiment was as before; the quantities were ·1 cc. of AS3 (sometimes +·1 cc. of IAS) + ·5 cc. of 1-100 dilution of NHS.

1. AS3+NHS . . .	·0150 cc.	precipitum
2. AS3+IAS3+NHS . .	·0160 cc.	,,
3. AS3+NRS+NHS . .	·0145 cc.	,,
4. NRS+NHS . . .	trace	,,
5. IAS3+NHS . . .	trace	,,

These results seem to indicate that with hæmatosera, at any rate, "precipitoids" are not formed when the antiserum is inactivated by heat, and agree with the observations of Michaelis.

* * * * *

It having been thought possible that an antiserum might give its maximum precipitate with the fluid employed in its production, the following experiment was made :—

Exp. 6.—Antisera were taken AS7 (serum, spheroidal cell carcinoma $\left\{\begin{matrix}10—10\\4—4\end{matrix}\right\}$; AS6 (pleural fluid, sarcoma $\left\{\begin{matrix}10—10\\4—4\end{matrix}\right\}$; AS4 (pleural fluid, spheroidal cell carcinoma $\left\{\begin{matrix}10—10—10—10\\4—3—4—3\end{matrix}\right\}$; and AS5 (pleural fluid, sarcoma $\left\{\begin{matrix}10—10—10—10\\4—3—4—3\end{matrix}\right\}$.

These antisera were tested against their own original fluids (OF), and against normal human serum, with the following results (·1 cc. + 5 cc. of 1-100 dilution) :—

1. AS7+OF	·0033 cc.	precipitum
AS7+NHS . . .	·0033 cc.	,,
2. AS6+OF	trace	,,
AS6+NHS . . .	·0058 cc.	,,
3. AS4+OF	·0025 cc.	,,
AS4+NHS . . .	·0058 cc.	,,
4. AS5+OF	·0091 cc.	,,
AS5+NHS . . .	·0150 cc.	,,

It will be noticed that with the exception of AS7 (an antiserum produced by serum) all the antisera used gave larger precipita with normal human serum than with their

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original fluid. It is noticeable, too, that AS4 is much weaker than AS5, although in both the animals had been treated with pleural fluid in the same quantities. The question as to whether this is due to a greater precipitin-producing power in one of the pleural fluids, or to individual peculiarity on the part of the rabbit, will be discussed later. As in all cases except AS7 the proteid content of the original fluid was less than that of serum, it is inferred that the larger precipitate is due to this fact.

In this connection further experiments were made in which the same antiserum was tested against different normal human sera.

EXP. 7.—The antiserum AS7 (serum, spheroidal cell carcinoma $\left\{\begin{matrix}10—10—10\\4—4—6\end{matrix}\right\}$ was used against the sera of 5 healthy males (·1 cc. + ·5 cc. of 1-100 dilution). Each result given below was the mean of two observations :—

AS7+D	·0037 cc.	precipitum
AS7+T	·0041 cc.	,,
AS7+W	·0048 cc.	,,
AS7+G	·0043 cc.	,,
AS7+C	·0043 cc.	,,

AGAIN, EXP. 8.—The antiserum AS5 (pleural fluid, sarcoma $\left\{\begin{matrix}10—10—10—10\\4—3—4—3\end{matrix}\right\}$ was used against normal human sera (·1 cc.+·5 cc. of 1-100 dilution).

AS5+D	·0115 cc.	precipitum
AS5+T	·0166 cc.	,,
AS5+W	·0175 cc.	,,
AS5+G	·0115 cc.	,,
AS5+C	·0125 cc.	,,

It will be seen from these two experiments that different normal sera give varying precipita with the same antiserum. This does not appear to be due wholly, at any rate, to the amount of proteid contained in the sera, as is indicated by the following experiment :—

EXP. 9.—Two of the sera used in the preceding experiments were taken, viz. D and T, the latter of which had

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been found to give in each case a greater precipitum than the former.

The specific gravity of each was estimated by means of the pycnometer, and was found in the case of D to be 1·0263, and in the case of T to be 1·0245. The two sera were again tested against AS5 (in quantities represented by ·4 cc. + 2 cc. of 1-100 dilution) with the result—

AS5+D	·0508 cc. precipitum
AS5+T	·0566 cc. ,,

It seems a not unreasonable assumption to suppose that the specific gravity of a serum runs parallel with its proteid content, and if this be so the above experiments show clearly that the varying amount of precipitum does not altogether depend on the amount of proteid present. That the latter factor, however, has a considerable influence is shown by Experiment 6.

* * * * *

An effort was made to explain the fact shown in Experiment 6 that AS4 was much weaker than AS5, although in both cases the animals had been treated with a pleural fluid and in the same quantities $\left\{\begin{matrix}10—10—10—10\\4—3—4—3\end{matrix}\right\}$. Was this due to individual peculiarity on the part of the rabbits, or was it dependent on the compositions of the pleural fluids? The latter, at any rate, was capable of investigation, and 10 cc. of each pleural fluid were diluted with distilled water, made slightly acid with acetic acid and boiled. The total proteids thus precipitated were washed on a weighed filter paper, dried at 100° C., and estimated gravimetrically. 10 cc. of each were again taken and saturated with magnesium sulphate to precipitate the globulins. The filtrate was then treated with acetic acid and boiled, and the precipitate (albumen) washed on a weighed filter paper, dried at 100° C. and estimated gravimetrically. The results of this analysis were as follows :—

	Pleural fluid producing AS4.	Pleural fluid producing AS5.
Total Proteid . .	3·34 per cent.	3·73 per cent.
Albumen	2·73 ,,	2·21 ,,
Globulin	0·61 ,,	1·52 ,,

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It will be seen that the pleural fluid producing the stronger antiserum was relatively much richer in globulin than the other.

This question has been worked at by several observers. Nolf* used horse serum, separated the globulin and the albumen, and injected each separately into rabbits. He found that the serum of rabbits injected with globulin rendered horse serum turbid and also globulin solution, but left albumen solution clear. Serum from rabbits injected with albumen, on the other hand, rendered turbid neither horse serum nor globulin solution, nor albumen solution. Nolf, therefore, concludes that the precipitin reaction is the response of the organism to the injections of a well-determined category of proteid substances of the blood, and that it is globulin only which produces it to the exclusion of albumen.

Le Blanc† obtained results contrary to Nolf. Using cow serum, he separated the globulin and albumen and injected each separately, but obtained a greater reaction with the serum of animals treated with albumen than with that of animals treated with globulin. Linossier and Lemoine‡ found that rabbits injected with serum albumen acquired a precipitating power, but in a less degree than animals injected with globulin. Falloïse§ inclines from experiments to the belief that to globulins alone is attributable the property of producing the precipitating power.

The experiment quoted is distinctly in favour of the view of the greater power of globulin in precipitin formation.

* "Ann. de l'Instit. Pasteur," xiv.
† "La Cellule," xviii.
‡ "Compt. rendus de la Soc. de Biologie," 1902.
§ "Ann. de l'Instit. Pasteur," xvi.

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CHONDRIFYING CARCINOMA.

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AMONGST 1,179 consecutive cases of malignant disease, 1,011 being of the nature of carcinoma and 168 of the nature of sarcoma, which have been treated in The Middlesex Hospital and investigated in the Cancer Research Laboratories during the five years 1900 to 1904, there have been three which are of special interest in connection with a comparatively rare type of malignant disease, chondrifying carcinoma.

In one of these three cases there was an extensive development of typical hyalin cartilage from the stroma of the recurrent growth after an operation for carcinoma of the rectum. In the second case a primary new growth in the testicle contained material of a cartilaginous nature, but the histological characters of the tumour were so obscured by degenerative changes that a diagnosis was only arrived at after a consideration of the character of foci of new growth in other parts, which appeared to be secondary to the testicular growth, and were themselves plainly carcinomatous. And in the remaining case a new growth which originated in the spermatic cord contained well-formed hyalin cartilage.

CASE I.

Columnar-celled carcinoma of the tubular type affecting primarily the lower end of the rectum; secondary invasion of the left inguinal glands; removal of the primary growth and diseased gland mass; recurrence of the growth, now showing chondrification of the connective stroma. (Cancer Register, 242/00.)

Mary M., aged 67 years, was admitted into one of the surgical wards under the care of Mr. Pearce Gould in January, 1900. On admission she was found to be suffering from a new growth which involved the lowest 3 inches, or so, of the

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rectum, it being possible to pass the finger well above the level of the growth. There was an enlarged and indurated gland in the left inguinal region.

The affected portion of the bowel together with the tissues round the anus were excised, and the infected tissues in the left inguinal region were removed as thoroughly as possible. The operation wounds healed up satisfactorily, and the patient was discharged from the Hospital.

In the following September the patient returned to the Hospital, and reported that the disease had recurred in the region of the perineum in May, and in the neighbourhood of the inguinal operation soon afterwards. The case was now such that no further relief by operation was possible. The woman was admitted into the special cancer wards and died there on the 30th November, 1900.

Examination after death.—The body was much wasted. The disease had extended from the two centres of recurrence, and the two areas having coalesced, there was now a large irregular ulcerated surface with hard and raised edges, appearing in the left inguinal region and extending downwards and inwards from the middle of the groin along the fold to the vulva, and thence backwards along the left labium to the coccygeal region behind the aperture of the bowel.

Underlying the ulcerated surface was new growth, whitish in appearance and of very firm consistence, although the presence of cartilage was not suspected at the time of the examination.

The upper end of the femur was invaded to a slight extent by the new growth, but there was no enlargement or thickening of the bone.

No other focus of new growth was present, and the cause of death was double purulent pleuritis, probably due to bacterial infection originating in the large ulcerated surface.

The Histological Appearances of the Growth.

The growth in the rectum removed during life.—Sections of the growth show the appearances characteristic of columnar-celled carcinoma of the tubular type, the epithelial cells of which have in many places undergone a mucoid (or

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colloid) change (PL. VIII. *Fig.* 1). The stroma is of the usual character. It shows a considerable quantity of elastic fibre; there is round-celled infiltration in places, and here and there are seen strands of tissue which have undergone a mucoid or myxomatous change, the individual fibres having a somewhat swollen appearance and being differentiated by the manner in which they take up the hæmatoxylin stain.

The microscopic examination shows that the new growth extends along the mucous membrane down to the skin of the anus, where the columnar-celled tubules can be seen almost in contact with the squamous epithelium of the margin of the anus.

The inguinal gland removed during life.—Sections of the affected gland removed by operation show the same kind of columnar-celled growth as that found in the rectum (PL. VIII. *Fig.* 2). In many of the sections the columnar cells have undergone an extreme degree of mucoid change, and can no longer be recognised in the tubules as epithelium. The appearance of the stroma of the new growth varies; in some places the stroma resembles generally that seen in the rectal growth; in other places the tissue has undergone a marked change, appearing as an homogeneous material with something of the appearance of ground glass, and showing but few nuclei. Tracts of the original lymphoid cells of the gland can be seen in places.

The recurrent growth as present after death.—Sections of various portions of the growth were examined after death, and the appearance, so far as the true carcinoma elements are concerned, is as before; the growth is obviously a columnar-celled carcinoma of the tubular type, and the epithelial cells generally show less tendency to mucoid change than was observed in the two previous sets of sections (PL. IX. *Figs.* 1 *and* 2). The stroma is in many places of the usual fibrous character, showing here and there myxomatous change; elsewhere considerable tracts of the fibrous stroma have been replaced by masses of pure hyalin cartilage. This cartilage is quite typical in appearance. The lacunar spaces usually contain only a single cell, but sometimes two are seen. The relationship of this cartilage to the fibrous stroma will be discussed further on.

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CASE II.

New growth of the right testicle; secondary growth in right spermatic cord, aortic glands, right ureter, spleen, liver, both lungs, and posterior mediastinal glands; primary growth in testicle contains cartilaginous material, and traces of epithelial cells can be seen, but histological characters are masked by hæmorrhage and extensive degenerative changes; secondary growth in liver shows advanced degenerative changes similar to those in the testicle growth; the spleen, both lungs, and the posterior mediastinal glands show a growth of columnar-celled carcinoma of the tubular type. (Cancer Register, 51/00.)

George H., aged 26 years, was admitted into the Cancer Wards of The Middlesex Hospital under the care of Mr. Henry Morris, on 2nd March, 1900. On admission the patient was found to be suffering from what was believed to be a sarcoma of the right testicle, the tumour being of considerable bulk and of extremely hard consistence; there was some thickening of the right spermatic cord. The patient was almost unconscious, and in a very serious condition generally, when admitted, and it was not possible to obtain any history of his illness either then or subsequently. Death occurred on 16th March, 1900.

Examination after death.—The body was fairly well nourished. There had been free development of gas after death in the liver, in the heart muscle, and in various other parts.

It may be stated here that a special bacteriological examination was not made, but that when sections of various parts were examined microscopically, it was found that generally they contained large masses of a rather long and fine bacillus which stained well by Gram's method. This bacillus was found in especially large numbers in the substance of the new growth of the testicle, in the new growth in the liver, and in the spleen. The appearances were such as to indicate infection before death; but in the absence of any proper bacteriological examination it was, of course, impossible to say whether these particular micro-organisms had any relation either to

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the apparent toxæmia from which the patient was suffering on admission or to the development of gas in the tissues after death.

The new growth of the testicle presented itself as an ovoid mass, with a smooth surface, measuring 4 inches in the longer and 3¼ inches in the shorter diameter; the weight was 18½ ounces. There was a single small cyst at the upper end; the greater part of the mass was deeply blood-stained, but whitish areas were to be seen here and there. The tumour was softened in places, but the bulk of it was of very firm consistence. The surface of the tumour was smooth, and the new growth appeared to be contained within a sort of fibrous capsule, which did not, however, strip off.

The right spermatic cord was thickened, and presented two isolated masses of what appeared to be new growth; the right ureter also contained two small similar nodules, but neither they nor the growth in the cord were examined microscopically.

There were several quite minute nodules of whitish appearance in the wall of the cæcum; these when examined microscopically appeared to consist mainly of lymphoid tissue.

In the lower part of the spleen there was a spherical mass of rather soft white growth, measuring about 3 inches in diameter.

In the liver there were two rounded masses of new growth; one in the right lobe measured about 1 inch in diameter, and was softened and deeply blood-stained; the other was a rather larger mass of whitish growth.

There was a largish mass of friable, pinkish-coloured new growth in the situation of the aortic glands.

The right lung contained a single mass of new growth which measured about 1 inch in one diameter and ¾ inch in the other, situated at the base and projecting into the pleural sac. The left lung also contained a single small nodule, situated in the lower lobe.

There were two masses of new growth in the posterior mediastinum, one of the size of a pigeon's egg, the other representing a single small infiltrated gland.

The pericardial, pleural, and peritoneal sacs each contained some quantity of turbid blood-stained fluid.

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The Histological Appearances of the new Growth.

Sections from the following material were prepared and examined: the testicle tumour, the new growth in the right lobe of the liver, in the spleen, in both lungs, and in the posterior mediastinal glands.

The new growth in the testicle.—On examining the sections, two parts of the tumour can be clearly differentiated, (1) an external capsular layer representing a thickened tunica albuginea, and (2) an internal mass of new growth.

The external capsular layer consists mainly of fibrous tissue, amongst which are to be seen some elastic tissue and isolated bundles of unstriped muscle fibre; the presence of the last of these being explained by a hypertrophy of the unstriped muscle fibres which Kölliker has described in the fibrous interlobular septa which pass into the tunica albuginea.

There is microscopically no sharp line of demarcation between this thickened fibrous layer and the degenerated mass of new growth underneath, and what appear to be solid columns of epithelial cells have invaded the fibrous layers in a few places.

The greater part of the mass of new growth within the external fibrous layers appears to be in an advanced stage of degeneration; it is permeated by extravasated blood, thickly invaded by bacteria of the bacillary type already mentioned, and but little of its proper structure can be made out.

There are large masses of amorphous granular material which scarcely stains with either hæmatoxylin or eosin, and there are also masses of a non-staining homogeneous material which from the appearance in sections is evidently very hard, having undergone fragmentation in parallel lines during the cutting of the pieces.

In addition to the above there is a quantity of what is apparently cartilage which is undergoing calcification. This occurs in two forms; first, there are masses of homogeneous material, with well-defined edge, which stain rather deeply with eosin and which contain what appear to be cartilage cells lying in lacunæ. The cartilage cells, however, are not very well defined, and the matrix stains rather more deeply with eosin than normal cartilage usually would. In other places

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there are trabecular masses of hyalin-looking material, slightly fibrillated in places, which stains very lightly with eosin, and which is probably hyalin cartilage which has undergone calcification. This tissue contains a very few cells of an ill-defined character, and presents numerous irregularly-shaped spaces which contain blood and which are lined by a fine wall of what appears to be condensed tissue, showing no nuclei. Under a low power of the microscope the appearance of the hyalin tissue and its trabecular arrangement closely resemble what is seen in a developing long bone in the trabecular zone, immediately beyond the zone of calcifying cartilage.

In addition to the tissue already described, there are collections of mono-nuclear cells, some largish and of oval shape, others smaller and round; and then again there are small oval, or round, masses, devoid of nuclei, which look like particles of amyloid substance and stain a brownish red colour with the eosin.

Briefly, the new growth in the testicle is represented by masses of degenerated, and in some places probably necrotic, tissue of which the only recognisable elements are some cartilaginous material; the appearance of what are probably epithelial cells in the innermost layers of the fibrous capsule suggests that the growth was originally carcinomatous.

The new growth in the liver.—The picture presented by sections of the growth in the right lobe of the liver is, again, one of advanced tissue degeneration. There are masses of non-staining homogeneous material which undergoes fragmentation in parallel lines on cutting, exactly similar to what was seen in the testicle tumour; and it may be mentioned that this material was so hard that the edge of the microtome razor was repeatedly broken when cutting the sections which show it. In addition to this homogeneous material the liver growth shows masses of débris, small round particles of what look like amyloid material, and in a few places masses of what is by its staining reaction evidently mucoid material.

The new growth in the spleen.—Here the character of the new growth presents no difficulty; it is that of a columnar-celled carcinoma with a very abundant fibrous stroma. The growth in the spleen was described in the notes made at the examination of the body as being of soft consistence, but

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there is no indication of degenerative change in the sections examined.

The new growth in the lungs.—In both lungs the new growth was that of a columnar-celled carcinoma of the tubular type, showing, however, many microscopic dilatations of the tubules. The fibrous stroma would be described as richly cellular, and there are indications of mucoid changes both in the epithelium and in the stroma of the growth. A single microscopic nodule of perfectly formed cartilage was found in one of the lung masses of new growth.

The new growth in the posterior mediastinal glands.—Here again there is no doubt as to the nature of the new growth, a typical columnar-celled carcinoma of precisely the same character as that found in the lungs.

In spite of the failure to identify the nature of the new growth in the testicle itself, there will probably be little difficulty in accepting the conclusion that it was a columnar-celled carcinoma which had undergone chondrification, and then degeneration and, in part, necrosis. This conclusion is the only possible one in view of the fact that one focus of what was clearly secondary new growth in the liver showed a peculiar degenerative change of exactly similar nature to one which had occurred in the testicle, whilst other foci of new growth showed the structure of a typical columnar-celled carcinoma.

CASE III.

New growth in connection with the spermatic cord; removal by operation; tumour shows characters of carcinoma; new growth of epithelial cells; mucoid change in stroma, and development of cartilage in stroma. (Cancer Register, 29/03.)

The patient, a carman aged 23 years, was admitted into The Middlesex Hospital under the care of Mr. Pearce Gould on 22nd January 1903. He presented a small hard tumour, about the size of a hazel nut, which was apparently attached to the right spermatic cord about 1 inch above the level of the testicle. The tumour was loosely attached, having a range of movement of about 1 inch upwards and downwards. The

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tumour did not appear to be connected with either the testicle or the vas deferens.

The following history was given: There was nothing suggestive of either gonorrhœa or other venereal disease; there had been no pain or trouble with micturition; and there was no history of any injury received. About one month ago the patient was sensible of sharp twinges of pain in his testicle, and on feeling the scrotum he perceived a small lump, described as being of the size of a marble, above the testicle.

The patient was kept in hospital for a couple of days; but there being some doubt as to the nature of the swelling he was discharged with instructions to present himself again.

The patient returned to hospital on 6th February; and as it then seemed that the tumour had slightly increased in size its removal was decided on. At the operation the testicle and cord were brought to the surface through a short incision; the vas deferens and spermatic artery were readily separated from the new growth, and, the tunica vaginalis having been opened, the tumour with the part of the spermatic cord to which it was attached were excised.

The tumour removed was of a pale brown colour, with strands of white fibrous-looking tissue intersecting its substance. It was of oval shape, measuring about $\frac{3}{4}$ inch in the longer and a little more than $\frac{1}{2}$ inch in the shorter diameter.

The operation wound healed up quickly, and the patient was discharged from hospital.

The Histological Appearances of the New Growth.

The new growth shows two chief constituents: (1) epithelial-like, or epithelial, cells arranged in narrow, branching cylindrical tracts which are enclosed within the alveolar spaces of (2) a connective tissue stroma.

The epithelial cells are for the most part spheroidal in shape; they contain largish nuclei, and as a rule resemble the specific epithelial cells of a spheroidal-celled carcinoma. But in some places the cells show a tendency to assume a cubical form, and there are appearances suggestive of commencing tubulation of the cell columns. In many places the nuclei stain a lightish blue colour with hæmatoxylin, and the cells appear to be in an early stage of mucoid change.

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The arrangement of the epithelial cells with regard to the stroma is typically alveolar; and the connective tissue consists of short spindle-shaped cells, which in many places present an advanced mucoid change and numerous microscopic masses of cartilage. The spindle-shaped cells have very distinctly elongated nuclei, and, the cells being closely set, the stroma generally has a richly nucleated appearance. The cartilage is disposed in an irregular manner throughout the sections, and has obviously developed from the spindle-celled stroma.

The change apparently occurs as follows: The spindle cells assume a myxomatous and somewhat swollen appearance, their outline becomes indistinct, and the individuality of the cells is lost, so that one finds masses of more or less homogeneous material which is of a dull red colour in sections stained with hæmatoxylin and eosin. This material appears fibrillated in places, and in places presents side by side two kinds of nuclei—the elongated nuclei of the original spindle cells, and others of spherical shape which lie in clear unstained spaces. A still more advanced stage shows typical masses of cartilage free from any elongated nuclei. In the sections which have been examined it would appear that there may be two somewhat different processes by which the transformation of the spindle cells into cartilage occurs. The first has already been described, and in this the cells which have undergone the "myxomatous" transformation referred to above, appear in sections stained with hæmatoxylin and eosin, of a reddish colour of much the same tint as that of the cartilage matrix when similarly stained. And the steps in the change from spindle cell to cartilage are precisely those which can be traced in the transformation of the connective tissue stroma which was observed in Case I. But there appears in this particular case to be a second method of transformation, in which what one may term a coarser mucoid change of the connective tissue precedes the development of cartilage. In sections stained with hæmatoxylin and eosin, in which the first process described can be observed, one also finds large coarse masses of almost amorphous material which stains a rich violet colour, and resembles the "colloid" material resulting from the mucoid change in epithelial cells, but which in this case is certainly formed in the stroma. In places this violet-

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staining mucoid material appears in masses by itself; in other places the mucoid material is being replaced by cartilage of exactly the same appearance as that which results after the more delicate "myxomatous" change described above.

The change involving the transformation of masses of the coarse mucoid material into cartilage progresses generally from the periphery of the mass into the interior; and so one finds masses of the violet-stained coarse mucoid material appearing as if embedded in cartilage, which is stained red by eosin and of the character already described.

It is, of course, probable that the two processes are essentially of the same nature, only progressing with different degrees of intensity; but I have not been able to trace any definite connection between them except that the preliminary change in the spindle cells is the same in either case. The important point, however, is that the end result with each is identical, and that in either case the development of the cartilage occurs solely in and at the expense of the connective tissue stroma; it is quite certain that the epithelial cells do not undergo any cartilaginous change.

Sections made at one edge of the tumour show muscular tissue, probably belonging to the cremasteric muscle, which is being invaded by the new growth. The new growth is certainly a carcinoma, but it is not certain from what epithelium it took origin.

On first examination one would say that the carcinoma was of the spheroidal-celled variety, for to that type by far the greater part of the tumour conforms. But on further examination one finds that in places the cells tend to assume a cubical shape, and in places one sees in cross section appearances which suggest commencing tubulation of the cylindrical tracts of epithelial cells. One sees, in fact, what is frequently observed at the growing edge of a columnar-celled carcinoma of the typically tubular type. Here, as for example in a carcinoma of the rectum, in the older portion of the growth one sees the appearance typical of this kind of carcinoma, tubules with a clear lumen and lined with columnar or cubical cells. But where the growth is invading the neighbouring tissues the outgrowth takes place by solid columns of spheroidal epithelial cells, which subsequently assume the cubical or

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columnar type as they arrange themselves round the lumen of the now tubular structure. And in doing this the cells of the new growth only repeat the habit of growth of their kind under normal circumstances. Thus, if one traces the development of a typical tubular gland, one finds that its development commences with a down growth from the surface of a bud or solid column of spherical cells. As the bud elongates a lumen is formed by a process of tubulation in the cell mass, and as tubulation occurs, the originally spheroidal cells, under the influence of altered conditions of mutual pressure, arrange themselves round the lumen of the gland and assume a cubical or columnar form.

Whilst, therefore, the appearance of this tumour conforms generally with that of a spheroidal-celled carcinoma, there remains a possibility that it really represents an early stage of a malignant new growth which has originated in a columnar epithelium, but in which tubulation of the processes of epithelial growth, with consequent alteration in the morphology of the cells, has not yet taken place.

The next point to be considered is the exact seat of origin of this tumour, which was not attached in any way to the vas deferens, but was lying loosely attached to the cellular tissue of the spermatic cord, a short distance above the upper end of the testicle. The only structure lying outside the vas deferens in this situation from which an epithelial new growth would be likely to take origin is a relic of the Wolffian duct, the parepididymis or Organ of Giraldés, which consists of several small irregularly shaped masses containing convoluted tubules, which are said to be lined by ciliated columnar epithelium. And, in spite of the difficulty arising from the apparent type of epithelium present in the tumour, it is to this relic that I would be inclined to attribute the origin of the new growth.

As malignant new growth originating in the structures of the spermatic cord is of rare occurrence, it will be worth while to mention a case described by Pepper (13) as "A case of myxo-chondro-sarcoma of the spermatic cord," which resembles in some particulars this Case III.

The patient was a man, aged 75 years, who first noticed a swelling below the left external abdominal ring in January,

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1884. The swelling underwent continuous increase up to the time of an operation in October 1884. The patient died a few days after the operation, but no examination of the body was made after death. The new growth is described as follows: "On dissection it was found that the tumour, which was completely encapsuled, was deeply grooved on its front part by the spermatic cord, but the cord and testicle were readily separable from it . . . When quite fresh the sectional surface presented a gelatinous, quivering appearance, very closely resembling that of a mucous polypus of the nose; but here and there were strands of denser white tissue, and tracts which could not be distinguished from a mixed or spindle-celled sarcoma . . . The microscopical characters were those of a connective tissue tumour; the greater part consisted of mucous tissue, showing a clear ground substance threaded by delicate fibres, and set with round, oval, angular and branching cells. One part, more opaque than the rest, was composed of round and spindle-cells, typical of a sarcoma, and embedded in this were microscopic islets of cartilage."

The points of resemblance between the tumour in this case of Pepper's and that in Case III. are so striking that one is justified in suggesting that the one apparently essential point of difference—the absence of the epithelial cells in the tumour which Pepper describes—may perhaps be explained by a destruction of the epithelial cells in the mucoid changes which were apparently much farther advanced in this case than in the other.

Chondrifying Carcinoma of the Testicle.

Most of our knowledge of chondrifying carcinoma is founded on cases in which the primary seat of disease has been in the testicle; although even with regard to this organ the pathology of the different varieties of malignant and other disease in which the formation of cartilage occurs has not yet been thoroughly elucidated.

If one searches the records of the oldest pathological society in existence, the Pathological Society of London, one finds during earlier years the occasional mention of tumours of the testicle which appear to have been of a malignant character, and in which cartilage was found.

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Thus in 1853 Jabez Hogg (8), an expert microscopist, records a case of "enchondroma of the testicle," following an injury in a man, aged 30 years. In a description of the microscopic appearances of the new growth it is stated that "all the nodules of cartilage found in the tumour were originally developed in the tubuli seminiferi." The after history of this case is given in a supplement to the volume of Transactions of the Society for 1882. The Council having made an inquiry, so far as was practicable, of authors who had published cases recorded in the first 31 volumes of Transactions, received the following note from Jabez Hogg (17) with regard to his patient: "W. W. died in about twelve months after the removal of the left testicle, of cancer of the kidney . . . the necropsy disclosed an enormous cancerous condition of the kidney on the same side (left) as that of disease of the testicle."

In 1855 Henry Thompson (15) gives an account of a tumour of the testicle removed from a man, aged 25, with the history of an injury 7 months previously as the probable cause of the new growth. The tumour was reported on by T. S. Curling and Andrew Clark, who agreed that the new growth presented in places the microscopic appearances of pure cartilage, and also state that it "contained semi-transparent rounded gelatiniform-looking masses, with minute spots of extravasated blood."

At about this time, in 1855, as Kanthack and Strangeways Pigg (9) point out, Virchow had observed the formation of cartilage in cancerous growths of the testicle, and, "while mentioning the combination of enchondroma with carcinoma, at that time (1855-1863) believed that the carcinoma cells had been derived from the cartilage cells by a progressive metamorphosis."

In 1867 De Morgan (5) published an account of a case in which a tumour developed in the right testicle of a man, aged 35 years, after severe bruising by the pommel of a saddle. Enlargement of the testicle was observed 2 months after the accident, when the swelling of the scrotum which occurred immediately after the accident had subsided; the testicle and tumour were removed six months later. In the description of the tumour removed by operation it is stated that numerous cysts were present, varying in size from that of a

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pea to that of a walnut, and that some of these cysts presented small solid ingrowths. In the walls of the cysts there were one or two small deposits of cartilage; the contents of the cysts included "granules, granular corpuscles, delicate corpuscles like those of mucus, nuclei, oil globules, and blood corpuscles." The septa enclosing the cysts were "composed mainly of connective tissue, the cysts having an epithelial lining."

Some 2 years later De Morgan (5) recorded the sequel of the case: the man returned to hospital in 1868, being then 38 years of age, with a large immovable tumour in the right side of the abdomen extending from a little below the liver down to the pelvis, and died in March, 1869.

At the examination after death it was found that the abdominal tumour consisted mainly of small and large cysts which contained various fluid and semifluid contents—in some there was a chocolate-coloured viscid fluid, in others clear viscid fluid, and in others "semi-solid white matter like soft boiled rice." A separate tumour, of the size of a small orange, also studded with cysts but with a well-marked cartilaginous stroma, was found in the right groin, attached to the upper part of the spermatic cord. And embedded in the lung substance there were found scattered cystic tumours—some twenty in all—varying in size from that of a pea to that of a hen's egg, some of which contained cartilaginous nodules and clear viscid fluid. The description given of the cartilage present is: "The structure of the cartilaginous nodules in the cysts of the lungs, as also in the abdominal tumour in the right groin, is that of a perfectly formed articular cartilage, consisting for the most part of perfectly round or oval cells in a dimly granular matrix, this being sometimes fibrillated. At some points, notably about the edges of the nodules, the cartilage cells are seen to change their plump round forms for oval and elongated spindle forms, and seeming to pass gradually into forms similar to those of investing connective tissue and sarcomatous growth." It is interesting to note that De Morgan clearly traces the gradation from the fibrous connective tissue stroma of the growth to the fully developed hyalin cartilage.

Coming to a later period, when the histological characters of carcinoma and sarcoma had been studied under modern

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conditions, we find in 1882 so skilled a pathologist as Butlin (2), whose teaching has had so far-reaching an influence in the formation of our conception of the nature of malignant disease, not only questioning the occurrence of chondrifying carcinoma of the testicle, but also omitting mention of the variety of carcinoma—the columnar-celled—in which this change is most likely to occur.

Thus Butlin writes with regard to carcinoma of the testicle: "Only one variety of carcinoma has been hitherto observed—the spheroidal or gland celled. This presents a decided alveolar structure, and the alveoli are filled with cells resembling the epithelium of the seminal tubes." And reference is made to a drawing which shows with clearness what one would term a typical spheroidal-celled carcinoma.

Butlin continues: "Carcinoma of the testicle is prone to fatty and caseous degeneration, and large portions of its substance may be thus destroyed. It rarely becomes organised, and apparently never contains cartilage, although Kocher (10) states that the combination with cartilage is more common than that of sarcoma with cartilage. It is difficult to understand whence this conclusion is derived, for I have not found a single case on record of a carcinoma containing cartilage, nor has an instance of the kind ever fallen under my observation."

Butlin gives a list of 61 cases of malignant disease of the testicle recorded up to 1881, which when analysed gives the following figures:—

	Total Number of Cases.	Number of Cases in which Cartilage occurred.
Carcinoma - - -	20	0
Round-celled sarcoma - -	22	0
Spindle-celled Sarcoma - -	13	7
Mixed-celled Sarcoma - -	6	1

Since Butlin wrote as above our knowledge of new growths of the testicle has increased so far that we can now say with certainty that two distinct varieties of carcinoma may affect the testicle, the glandular or spheroidal-celled and the columnar-celled. And one can now see that a chondrification of the fibrous stroma of the columnar-celled new growth is not

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uncommon. In fact, we may suspect that Kocher was not far wrong when he asserted that in the case of the testicle the occurrence of cartilage is more common in carcinoma than in sarcoma. And I think that when all the facts have been considered it will seem highly probable, even certain, that some at any rate of the cases which Butlin placed on his list amongst the spindle-celled sarcomata, and in which cartilage was present—and amongst these I would mention De Morgan's case which has already been referred to—were really cases of carcinoma in which the specific epithelial elements had either been overlooked, or their import not understood as we would understand it now, and in which the adventitious connective tissue stroma was taken to be the essential tissue of the new growth.

The following, amongst cases already recorded, may be quoted as examples of chondrifying columnar-celled carcinoma of the testicle :—

First must be mentioned the celebrated case of a cartilaginous growth in the testicle, with secondary nodules of cartilage in the lungs, described by Paget (11) in 1855, and repeatedly referred to since then by writers on pathology as an example of a malignant enchondroma. And the case is so striking an example of the enduring value of accurate observation in pathological science, in which mere opinions change from year to year, that I may be excused if I quote it at some length.

The case was that of a man, aged 37 years, who was admitted into St. Bartholomew's Hospital, on 5th January, 1855, with a large tumour of the right testicle, which measured 10½ inches in circumference and involved the spermatic cord. Some swelling of the testicle had been noticed first two years previously, at about the time when the patient had received a severe injury to the back and right thigh from the fall of a sack of corn ; and a year later the testicle had been severely bruised by a fall on a bar of iron. The testicle tumour and the cord were removed at the level of the internal inguinal ring, and the patient left hospital in the beginning of April. He was re-admitted towards the end of the month with signs of lung disease, and died on the 1st May.

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At the examination after death it was found that from the scar at the internal ring "two dilated and tortuous lymphatic vessels passed upwards and backwards with the spermatic vessels," presenting in their course nodular enlargements, and terminating in a mass of new growth of the size of a hen's egg, which was adherent to the inferior vena cava close to the termination of the renal veins. At this spot the new growth had invaded the wall of the vein and projected into the channel; there were also two small independent masses of new growth on the wall of the vein in the neighbourhood. In many of the larger branches of the pulmonary artery "small shrub-like growths of cartilage, like that in the vena cava inferior, were attached to the lining membrane." Both the lungs contained numerous masses of cartilage of various size, the largest nodules being 1½ in. in diameter; the lungs together weighed 11½ lb. No other parts were found affected by the new growth.

In his histological description of the new growth Paget says: "The cartilage, in every seat of its growth, was of the true or hyaline kind; and in various specimens appeared to differ only according to the degree of its development. . . . In the less firm specimens of cartilage, and in those which were scarcely firmer than jelly, there could be found, I think, all the graduations of the development of cartilage. . . . I will only say that I found no structures which might not fairly be regarded as cartilage in some state: none of which a suspicion of cancer could be entertained." Paget's description so far applies to the cartilaginous parts of the new growth. But "the opaque-white and softer structures with which, in various shapes and plans, the cartilage was clustered in the lymphatics high up in the spermatic cord, and in some branches of the pulmonary artery, showed generally a filamentous and nucleated substance. Many of these growths had a minutely lobed, acinous, or foliated appearance. . . . Moreover, on some of these lobular and acinous growths there were corpuscles like those of a cylindriform epithelium." Paget gives a drawing which shows a row of typical columnar epithelial cells, and adds the description, "Cells like those of cylindriform epithelium from a growth in one of the lymphatics of the testicle": he also refers to a case of cystic disease of the

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testicle which was recorded by Curling (4) and in which Quekett had demonstrated the presence of cylindrical epithelium in some intracystic growth.

It will be seen that Paget recognised the presence of the columnar epithelium in the secondary growths, but, as might be expected, attached the chiefest importance to the cartilaginous element of the tumour.

The merit of pointing out the true nature of this case of Paget's belongs to Kanthack and Strangeways Pigg (9), who re-investigated the specimens obtained from this patient after they had rested for forty years in the museum of St. Bartholomew's Hospital. Kanthack and Strangeways Pigg showed that the testicle tumour presented unmistakable evidence of the growth of a columnar-celled carcinoma, and that new growth of the same kind could be found in the lymphatic glands, in the growth which had invaded the wall of the inferior vena cava, and in the lungs.

Poland (14) has recorded the case of a man, aged 24, who, when he came under observation, had noticed a swelling of the right testicle for four months. The testicle tumour was of the size of a bantam's egg, of hard consistence, and nodular surface: the spermatic cord was not thickened: there was no history of injury.

After removal of the testicle two well-defined nodules of new growth were found in the body of the gland, both of which contained numerous small cysts. Behind the body of the testicle there was an irregular mass of red spongy new growth. Microscopically the new growth was a columnar-celled carcinoma of the tubular type, and in the stroma of the mass of reddish new growth which was situated behind the testicle one or two small nodules of cartilage were seen.

Caddy (3) has recorded the case of a man, a European living in Calcutta, and aged 29 years, who suffered from a chondro-carcinoma of the right testicle. The history of the case was, that in December, 1884, the patient was struck on the right testicle by a cricket ball. Apparently there was no alteration in the gland until a week later, when some hardness was felt about the testicle. No further change occurred until October 1895, when the testicle began to increase in size. Caddy first saw the patient in September 1896, when

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the testicle was of about the size of a duck's egg, hard and painless. There had been no apparent increase in the size of the gland recently, and it was decided to keep the case under observation for a time. In November 1898 the patient, for the first time, began to feel pain in, and tenderness of, the swelling; and the swelling suddenly began to increase in size. In December, Caddy removed the testicle; the patient made a good recovery, and was well twelve months afterwards.

The testicle tumour "was the size of a shut fist. When it was laid open vertically, no testicular tissue was apparent to the naked eye, and the whole gland appeared to be infiltrated with a growth. At the upper and back part a nodule of cartilage was cut through, the size of a nutmeg." The specimen was examined by Major J. F. Evans, I.M.S., Professor of Pathology at the Calcutta Medical College, who in a short description states that the growth is a chondro-carcinoma, and that the nodule of cartilage "is surrounded and interrupted by many cysts lined by columnar epithelium."

To complete for the time the description of columnar-celled carcinoma of the testicle I may add some details of two cases of this variety of new growth in which the formation of cartilage was not observed, but in which there was present the mucoid, or myxomatous change in the fibrous stroma which I have described as being the stage preliminary to the development of cartilage. The two cases are also of interest when quoted side by side, as showing a marked difference in malignancy, although the new growth was of the same histological character. The first of the two cases is one recorded by Kanthack and Strangeways Pigg (9). The patient was a man, aged 24 years, who died with a malignant new growth of the right testicle. The tumour of the testicle was of the size of a goose's egg; it is described as being cystic, but the cysts were small, and not numerous, on macroscopic examination. The vas deferens was filled up with new growth. "The whole of the posterior wall of the abdomen in the lumbar region was occupied by a large malignant mass, evidently due to secondary deposits in the lumbar and aortic glands, which was continuous with the right testicle by a thickened cord, in which were seen dilated lymphatic vessels and enlarged lymphatic glands at intervals. . . The

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whole of the posterior and superior mediastinal glands along the course of the thoracic duct were the seat of considerable deposits of malignant material. . . The left supra-clavicular and cervical glands were enlarged by secondary deposits. . . The right lymphatic glands of the neck were slightly enlarged, and apparently the seat of secondary deposits." In both lungs there were numerous small nodules of new growth, about half-an-inch in diameter: the liver showed many secondary deposits, some of which were of the size of a pigeon's egg; and a mass of new growth was found in the right side of the heart, fixed to the free border of the tricuspid valve.

Histologically the new growth was typically that of a columnar-celled carcinoma, presenting tubules, alveolar spaces, and microscopic cysts lined by the epithelium. In the testicle tumour, and in a majority of the secondary foci which were examined, the carcinoma was of a definitely cystic character, the spaces sometimes being filled with mucous material. In many places the specific epithelial cells showed various stages of mucoid change. The stroma is described as consisting of "soft, or young cellular fibrous tissue," and was richly nucleated. The cells were spindle-shaped for the most part, and generally closely packed, but in some parts the spindle cells were less closely packed, and there resembled myxomatous tissue.

The next case is one which was histologically of a similar nature, but which clinically represented a somewhat lower grade of malignancy, the patient being apparently quite well some sixteen months after the removal of a large mass of carcinomatous lumbar glands by operation.

The patient, a man aged twenty-eight years, was admitted into The Middlesex Hospital (Cancer Register 61/95) under the care of Mr. Henry Morris in March 1895.

On admission the patient presented an abdominal tumour, deeply situated, which extended from the level of the lower costal cartilages on the left side to the level of the umbilicus.

The history given was that, two years previously, the left testicle had been removed because of a new growth, described as an "adeno-sarcoma"; no further trouble had occurred until about one month before his admission into The Middlesex

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Hospital, when the patient noticed the abdominal tumour for the first time.

An operation having been decided on, an incision was made along the middle line from the ensiform cartilage to the umbilicus. It was found, however, that the tumour was situated behind the peritoneum, so the patient was turned over, and a long incision was made in the lumbar region parallel to the last rib on the left side. Through this incision a largish mass of new growth was removed. The new growth consisted of three closely attached masses; the largest was of oval shape, measuring 4 inches in the vertical diameter, 2½ inches in the transverse diameter, and 2 inches in thickness from before backwards. The two other masses were smaller, each being of about the size of a small orange. The masses of new growth were apparently encapsulated, and contained numerous small cysts.

The patient was discharged from hospital after a satisfactory convalescence. He returned to hospital in July 1896, in a hypochondriacal condition, and complaining of constipation; but a careful examination failed to discover any evidence suggestive of recurrence of the disease, or indeed of bodily illness of any kind.

On microscopic examination the new growth removed by operation, is seen to be a columnar-celled carcinoma presenting a cystic appearance. There are numerous spaces which are lined by columnar epithelial cells, and a connective tissue stroma; a few slender columns of spheroidal epithelial cells can also be seen. Some of the epithelial-lined spaces are filled with mucoid material; and some of the larger spaces thus filled have lost all trace of the epithelial lining. In the largest of the spaces, such as would be obvious macroscopically, small processes of the stroma, supporting columnar epithelium, can occasionally be seen projecting into the lumen of the space. In places the epithelial cells show a distinct mucoid change. The connective tissue stroma varies in character in different parts of a section; generally it consists of rather loose nucleated fibrous tissue, but in places the cell elements are more closely set, so that tracts of tissue here and there would be described as richly cellular. The stroma is well supplied with blood vessels, and in one or two places small

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extravasations of blood can be seen. Some of the connective tissue shows commencing mucoid, or myxomatous, change.

Whilst the number of cases of malignant disease of the testicle which have been definitely described as cases of columnar-celled carcinoma is but small, there can be no doubt but that many other cases have been observed and recorded under other names; usually they have been described as cases of sarcoma, cystic sarcoma, or adeno-sarcoma.

It has been already said that in the records of earlier days one finds mention made of tumours which were of a malignant character, and which contained cartilage. One can go further, and say that in some cases the malignant disease was a columnar-celled carcinoma; and this in spite of the wide difference between the state of pathology at the present day and as it was at the period referred to, some fifty years ago. Paget's case of malignant disease of the testicle has been already related, and I may also call attention to some "Observations on Cystic Disease of the Testicle," published by Curling (4) in 1853, observations so accurately made, and so carefully recorded, that they are still of distinct value for the present purpose. Curling commences his paper:—"There is no disease affecting the testicle which appears to be less understood than the cystic, various opinions being entertained both of its nature and mode of origin. This obscurity has arisen chiefly from the late period of the disease at which the morbid specimens are examined; for, as they are obtained only after an operation which the surgeon delays until considerable disorganisation has taken place, the pathologist rarely possesses the opportunity of making an investigation in the early stage of the cystic development." A description is then given of the tumour from a case of cystic disease in a comparatively early stage, the testicle having been removed from a man, aged thirty-seven, in whom the growth had been noticed first some seven months before the operation; the only item of after-history given is that the man was in good health some six months later. Curling describes the cystic character of the new growth:—"The origin of the cysts in a dilatation of the tubes was clearly made out. Thus, in some specimens, a tube could be traced to a termination in a

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dilated pouch. In others a cyst appeared to arise from a lateral dilatation of a columnar tube, or at the extremity of a loop, whilst in others the dilatation appeared to be uniform. These dilated tubes and cysts were lined by a tesselated epithelium, and many of them contained a dark granular matter. The opaque whitish substance found in several of the larger cysts consisted of modified tesselated epithelial scales. The cysts containing this white matter were firmer and denser than the others. . . . This tumour must be regarded as the ordinary cystic disease, and the minute examination fully establishes the origin of the cysts in a morbid condition of the ducts. . . . It being clear that neither the tubuli seminiferi nor the ducts of the epididymis are the tubes which undergo these changes, constituting the cystic disease, its seat may be considered as conclusively traced to the ducts of the rete testis." Curling had noticed in other similar cases the occurrence of solid intra-cystic growths which, in one case, on examination by Quekett, "were found to possess a cellular structure, and to be covered on the surface with cylindrical epithelium, like that covering the villi of the intestine." When examining specimens of cystic testicle, Curling had "frequently remarked the occurrence of small masses of enchondroma mixed up with the morbid growth"; he says that recent observations had made it clear that the enchondroma is originally formed within the tubes, although he himself formerly, when describing these masses of cartilage, had stated "that they appeared to be contained within the cysts; but I believe that they are developed externally." But, as a matter of fact, Curling's original observations with regard to the seat of development of cartilage being outside the epithelial formation were quite correct.

Curling sums up the results of his observations thus:—

"The following are the propositions resulting from the preceding inquiries:—

1. Cystic disease of the testicle occurs in two forms, an innocent and a malignant.
2. Both forms are the result of morbid changes in the ducts of the rete testis, this part of the gland being the sole seat of the disease.

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3. The innocent form of the cystic disease is characterised by the presence of tesselated epithelium in the cysts.
4. The malignant form is characterised by the presence of nucleated cancer cells in the cysts.
5. Enchondroma occurs in both forms of the cystic disease, and almost constantly in old cases of the innocent, the cartilage being developed within dilated tubes."

A careful perusal of Curling's paper will show, without much doubt, that his malignant cystic disease of the testicle was what we would now term a columnar-celled carcinoma.

Coming now to work which must be judged strictly by the standards of modern pathology, I may refer to a paper on "Cystic Tumours of the Testicle," published by Eve (6) in 1887.

Eve's paper was based on a careful examination of twelve specimens of cystic new growth of the testicle, and contains a table including 28 other recorded cases of the kind in which a detailed microscopic examination has been made. Innocent and malignant cystic new growth of the testicle are recognised. "These tumours may be divided into two well-marked groups—the innocent and malignant, or cystic fibromata or sarcomata. To these a third may conveniently be added, having characters often intermediate between them, and may be termed cystic myxomata or myxo-fibromata."

The number of cases amongst the total of 40 in which the new growth contained cartilage was as follows:—The simple, or innocent, tumours including cystic fibroma, cystic myxo-fibroma, and adeno-fibroma, and the cases of malignant new growth being variously described as sarcoma, cystic sarcoma, cystic myxo-sarcoma, chondro-sarcoma, and "cancer":—

	Containing cartilage.	No cartilage.	Not mentioned.	Containing bone.
Simple new growths (21)	12	5	3	1
Malignant new growths (19)	12	3	4	—

Eve gives a careful description of the innocent tumours, the common cystic fibroma, or adeno-fibroma, of the testicle:—"In nearly all examples of cystic fibroma there are some cysts

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or tubules, especially the small ones, lined with longer or shorter columnar epithelium. In two typical examples from adults I found ciliated columnar epithelium. . . . Changes are evidently brought about in the character of the epithelium by pressure. . . . In explanation of the occurrence of several layers of flattened epithelium in some of the cysts and tubules, it may be thrown out as a suggestion that the superficial cells are flattened from pressure; and this is the more probable as the flattened cells occur in the larger cysts and tubules."

The changing morphology of the epithelial cells which Eve here refers to in part is exactly what one expects under the conditions, from what is known of the habit of growth of the normal cells. As has already been pointed out, in a new growth arising from a columnar epithelium there is first a budding-out of a solid column of spheroidal cells, then there is tubulation of the column, and the cells assume a long columnar form as they arrange themselves round the narrow lumen of the tubule. As the lumen increases, and possibly as the pressure of accumulating secretion in the closed system of tubules augments, the columnar cells give a little, and assume a cubical form; when the lumen has widened still more, and pressure has still increased, one finds the flattened type of epithelial cell which occurs in the outermost layers of the so-called cholesteatomata which are sometimes met with in both simple and malignant cystic disease of the testicle.

Referring to the cases of malignant new growth, the "cystic sarcomata" of the testicle, Eve says: "The epithelial lining of the cysts, so far as I have been able to observe, does not differ essentially from that of the fibromata. It is often mixed, but columnar epithelium predominates over the laminated form, whilst the reverse is the case with the fibromata. This may be due to the fact that the growth of the tumour is more rapid, and, therefore, there is less time for the expansion of tubules by an accumulation of fluid and consequent flattening and lamination of epithelium."

Eve describes the stroma of these tumours as being of various character: "It may be composed of round, or round and spindle-celled tissue, of fasciculi of spindle cells alone,

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or intermingled with fibrillar connective and myxomatous tissue, or again of fibro-sarcomatous tissue. Myxo-sarcomatous tissue is commonly present, either forming a considerable part of the tumour or distributed in scattered patches."

Eve formulates his conclusions as follows:—

"1st. There is no genetic difference between the innocent and malignant cystic tumours of the testicle; they are merely varieties of the same form of tumour.

2nd. The tumours originate in the hilum of the testis.

3rd. There is evidence of a new formation in these tumours of highly organised epithelial tissue, and it is therefore convenient, for anatomical classification, to describe them as adeno-fibroma, myxoma, or sarcoma, as the case may be.

4th. That the prototype of the epithelial formations is found in the tubules of the vasa efferentia and rete testis.

5th. There are grounds for believing that the tubules and cysts originate in certain elementary outgrowths from or rudiments of the Wolffian body existing throughout life in the hilum testis.

6th. But it is incorrect to say that they are derived from the organ of Giraldés, for these tubular remnants of the Wolffian body are situated between the testicle and epididymis, and altogether outside of the testicle. Besides, the cystic disease is produced, not merely by a dilatation of pre-existing tubules, but by a new formation of epithelium."

I have quoted Eve's paper at some length, for the reason that I can bring forward no better form of argument in proof of my assertion that chrondrifying columnar-celled carcinoma of the testicle has hitherto been usually described as sarcoma of that gland. Eve describes with convincing lucidity and accuracy a malignant new growth of the testicle originating in the epithelium of the tubules of the vasa efferentia and rete testis, but follows preceding pathologists in classifying it amongst the connective tissue, or mesoblastic, new growths as a sarcoma.

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At first sight it is not quite obvious why this error in nomenclature should have prevailed; in many of the cases which have been described as cases of sarcoma the essentially epithelial character of the secondary growths would seem to be self-evident, and most writers on tumours of the testicle since the distinction between carcinoma and sarcoma has been established on a satisfactory genetic and histological basis have commented on the fact that many of the cases of "sarcoma" of the testicle resemble rather cases of carcinoma in their general features.

Perhaps some explanation of the error may be found in the fact that these cases of columnar-celled carcinoma of the testicle frequently occur at ages earlier than those at which one generally finds carcinoma elsewhere, and also in the somewhat remarkable character of the connective tissue stroma present in the majority of these cases.

With regard to age, a study of recorded cases will show that columnar-celled carcinoma of the testicle does undoubtedly tend to occur at much earlier ages than those which one usually associates with the incidence of epithelial malignant disease. R. W. Parker (12) has recorded a case of "Congenital Sarcoma of the Testicle," which I take from the description to have been a case of columnar-celled carcinoma, in which enlargement of the testicle was noticed at birth, the infant being operated on when only a few months old. Eve gives the mean age of thirteen adults in his list of cases of cystic sarcoma as being 29½ years, and the early age in Kanthack and Strangeways Pigg's case of carcinoma, and also other cases which I have referred to, will have been noticed. And it is just worth pointing out that the columnar-celled variety of carcinoma generally seems to have a greater tendency to occur in comparatively young adult life than the others.

But perhaps the chief reason for the confusion of nomenclature has been that the attention of pathologists has been specially directed to the adventitious connective tissue (mesoblastic) stroma of the epithelial new growth by the character of the changes which may occur there; the stroma may present appearances markedly suggestive of growth-activity, tracts of round cells and tracts

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of closely packed spindle cells, and may further present evidence of activity in the direction of a development of a higher tissue from these indifferent mesoblastic cells, the development of cartilage after a preliminary myxomatous change.

This evolution of the adventitious stroma of the carcinoma will, I think, on further consideration prove not to be primarily due to any inherent properties of the mesoblastic tissue cells, but rather to occur in indifferent cells in response to a stimulus originating in the specific epithelial cells of the new growth.

Columnar-celled carcinoma of the testicle, then, may be said to present certain more or less distinctive characters: it frequently occurs unusually early in life as compared with epithelial malignant disease generally, and peculiar changes leading to chrondrification of the stroma are prone to occur. In addition to chrondrification of the stroma, columnar-celled carcinoma of the testicle shows in a marked degree the tendency to mucoid change, both in the epithelial cells and in the connective tissue stroma, which is often found in columnar-celled carcinoma of other parts. Cyst formation is also a characteristic feature; generally the cysts are formed by a dilatation of the newly formed epithelial tubules, possibly also sometimes by degeneration and softening of tracts of the stroma. Extravasation of blood into the substance of the new growth is liable to occur, probably in consequence of mucoid changes affecting the walls of the blood vessels.

It is probable that the malignant epithelial growth originates in the tubules of the rete testis or in the vasa efferentia; and the same structures may be the seat of a simple form of new growth, the relationship of which to the carcinomatous new growth is similar to that existing between simple adenoma and columnar-celled carcinoma of the colon, or between simple adenoma and glandular-celled carcinoma of the breast.

And the simple form of new growth originating in the rete testis presents peculiarities in its stroma comparable with those found in the carcinomatous new growth—myxomatous change and the development of cartilage.

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THE NATURE OF THE PROCESS OF CHONDRIFICATION IN CARCINOMA.

Whilst chondrification of the connective tissue stroma is apparently of somewhat frequent occurrence in columnar-celled carcinoma of the testicle, it has been but rarely described in association with carcinoma elsewhere. In the present paper chondrification of the stroma has been described in carcinoma originating in two other situations, the spermatic cord and the rectum. Carcinoma growing primarily from the spermatic cord is itself so uncommon that one cannot say anything as to the relative frequency of chondrification in such a tumour; the interest of the case lies mainly in the fact that the new growth probably originated in the cells of the organ of Giraldés, a relic of some tubules thrown out from the Wolffian duct, and that these cells are genetically closely related to the cells in which the chondrifying carcinoma of the testicle originates—the cells of the tubules of the rete testis or of the vasa efferentia, developed from a portion of the Wolffian duct. With regard to the chondrification of the carcinoma of the rectum, one can only say that such development must be of extreme rarity in this not uncommon kind of new growth.

Before proceeding to a consideration of the significance of the chondrification which has been observed in these cases, I may advert to certain cases of malignant growth of the parotid gland and of the kidney in which myxomatous tissue is frequently present, and associated occasionally with the development of cartilage. With regard to the malignant growths of the parotid gland I have nothing to say now, beyond pointing out that although they are commonly described under the names sarcoma or endothelioma, it is not by any means certain what their real nature is; in some cases it would appear highly probable that they are of epithelial origin and should be classed amongst the adenomata or carcinomata, as the case may be. Nor am I prepared at the present time to discuss the nature of certain new growths of the kidney which have been variously termed adeno-sarcoma, chondro-myxo-sarcoma, and carcino-sarcoma; I will content myself with pointing out that some of these

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cases bear a remarkable resemblance to those of columnar-celled carcinoma of the testicle. Thus the new growth originates in cells derived from outgrowths from the Wolffian duct, and frequently develops at an early age. Histologically, the primary tumour and secondary formations of new growth show columnar or cubical epithelium, in tubular arrangement, supported by a connective tissue, or mesoblastic stroma. The stroma may show constituent elements as varied as those found in the new growth of the testicle—round and spindle cells, myxomatous tissue, and cartilage.

In connection with the development of cartilage in the substance of a carcinomatous new growth, there are two main points which would appear to require investigation :—

1. As to the histological development of the cartilage, and its relation to the specific epithelial elements of the carcinoma ; and
2. As to the cause exciting the development of the cartilage.

With regard to the first matter, the histological development of the cartilage, it would seem clearly evident that the cartilage is developed directly from the connective tissue stroma ; and the stages of the development could be plainly traced more especially in sections made from specimens taken from Case I. One could trace the transition from spindle-celled connective tissue to a rather delicate myxomatous tissue, and from the latter to cartilage. In the transition from myxomatous tissue to cartilage, the somewhat hyalin-looking strands of tissue assume a swollen appearance, and individual fibres appear to coalesce one with another ; the elongated nuclei of the original spindle-cells gradually disappear, and typical cartilage cells replace them in the now more or less homogeneous hyalin matrix. And by the progressive transformation of this myxomatous tissue continuous tracts of cartilage of considerable extent may be formed around, and embed, the epithelial tubules. It seems also as if the development of cartilage occurs especially where the stroma is most vascular, and now and again one can see small blood vessels completely embedded in the developing tissue.

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The appearance of the myxomatous tissue is in every respect identical with that of the fœtal myxomatous tissue in which the cartilaginous matrix of bone is laid down. This statement as to identity of appearance was founded on a careful comparison of the myxomatous tissue in sections from Case I. with the tissues in sections of an early fœtus showing the development of the cartilage of the permanent vertebræ. And on subsequently reading Eve's paper it was found that the same comparison had occurred to him; referring to the development of cartilage in the stroma of "cystic fibromata" of the testicle, Eve writes: "The growth of the nodule takes place at its periphery, where there is a thin layer of myxomatous-looking tissue; and the manner of the transformation of this tissue into cartilage reminds the observer of the mode of formation of fœtal cartilage from embryonic cells as, for example, in the protovertebræ."

It may be stated with some confidence that there is no histological connection whatever between the cartilage and the epithelial cells. That is to say, the cartilage replaces only the connective tissue round the solid cell-columns or tubules, as the case may be; and a prolonged search through a large number of sections made of specimens from Cases I. and III. has failed to discover any indication that the cartilage ever invades, much less grows from, the epithelial structure, although in places the tubules can be seen completely embedded in a mass of cartilage (Pl. IX. Fig. 1). This point is of some importance, as Ziegler (16), apparently following Virchow, states that the patches of cartilage in chondrocarcinoma of the testicle sometimes break into the lymphatics and tubuli seminiferi, and there increase, producing ramifying forms. On the contrary, it would seem certain that no active proliferation of the cartilage, as such, takes place; the cartilage simply replaces the connective tissue stroma by a regular process of development, and it never assumes the independently malignant character which Ziegler's description would seem to imply.

The question which now remains for consideration is as to the reason for the occurrence of a process of chondrification in the stroma of an epithelial new growth, as to the exciting cause which determines the development of cartilage from the

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indifferent cells of mesoblastic origin, which form the adventitious connective tissue stroma of the carcinoma.

In explanation of this phenomenon two suggestions have been put forward, one that the formation of cartilage from the mesoblastic tissue is a result of an inflammatory reaction occasioned by the presence of the foreign epithelial cells, the other that the cases are examples of mixed malignant growth, epithelial and mesoblastic cells growing in some sort of harmony, but independently, side by side.

To the first suggestion the objection must be raised that whatever the appearances may have been in some cases, in others there is no indication of any inflammatory reaction, and, therefore, for this reason alone, the explanation is not valid for all cases.

The other explanation, that the growth is of mixed specific origin, is implied by the use of the terms "adeno-sarcoma" and "carcino-sarcoma," which have been applied to this type of malignant disease. At the present time, however, there are but few pathologists, I think, who would countenance the use of such terms as these, or, who would advocate the theory which the use of them implies.

Holding, as most do, that carcinoma is a specific growth arising in epithelial cells, that sarcoma is a specific growth from mesoblastic cells, and that all secondary formations of new growth are derived from cells originating in the primary growth, the theory of "mixed" malignant new growth is almost impossible, involving as it does the travelling in couples of epithelial and mesoblastic cells from the primary tumour to the site of the secondary formations. In exceptional cases, of course, as when small masses of growth are transferred from one point to another when a carcinoma invades the channel of a vein, a fragment of the adventitious mesoblastic stroma of a carcinoma may accompany the specific epithelial elements from one formation to another, but the theory of mixed malignant growth implies a good deal more than this.

Nor, again, is it possible to accept the theory, at one time brought forward, with the great authority of Virchow, that a development of epithelial cells from the specific mesoblastic elements of a sarcoma can occur. I do not think that one could deny the possibility, at any rate, of the development of

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cells of a mesoblastic type from epithelial cells, although, so far as I am aware, one has no evidence of its occurrence in post-natal life, but the reverse transition of mesoblastic tissue into epithelium appears to be impossible even in theory. When, therefore, to take the simplest case, one finds that a primary growth in the testicle, or in the kidney, contains epithelium of the types normal in those organs, and when one finds in either case that such epithelium recurs in a secondary growth in the lung, one is, by that fact alone, justified in describing the growth as a malignant epithelial one—as a carcinoma—whatever the character of its mesoblastic stroma may be. And whatever the character of the mesoblastic stroma of the secondary formation may be one is not justified in describing it as sarcomatous tissue, from the histological appearance alone. When the cell elements of the connective tissue stroma show evidence of growth-activity one may say that the tissue resembles that of a sarcoma, but the resemblance does not endow the cell elements with the properties peculiar to malignancy, nor does the resemblance justify the use of such terms as "carcino-sarcoma." There is, in short, no certain histological criterion of cell-malignancy; the epithelial cell of the carcinoma presents no feature of absolute distinction from its normal prototype, nor can we differentiate by histology alone between the cell of a sarcoma and analogous mesoblastic connective tissue cells. If, then, one cannot accept either the theory of the inflammatory origin of the cartilage, or the theory of "mixed" malignant new growth, what explanation of the development of cartilage in the stroma of these cases of carcinoma can be offered?

One might offer, at least, two other explanations: one might suggest that the development of cartilage is due to some inherent and spontaneous activity of the indifferent mesoblastic cells of the stroma, an activity tending to a development to higher tissue and due to some idiosyncrasy of the individual patient; or, on the other hand, one might suggest that the development of cartilage from the mesoblastic cells is due to some influence, some specific stimulus, emanating from the epithelial cells of the carcinoma.

With regard to these two possible explanations, there is not very much that could be said in favour of the first,

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except, perhaps, that the chondrification occurs in a variety of carcinoma which, as compared with other varieties, is especially liable to happen in early life, probably it may be even congenital. And one might suppose that at the early ages at which this variety of carcinoma sometimes occurs the connective tissue elements generally would be in a state of activity, which might well be shared by the stroma of any epithelial new growth.

But, it appears to me, there are some highly suggestive facts which may be cited in favour of the possibility of the alternative explanation, that is to say, that the development of cartilage from the mesoblastic cells of the stroma occurs in response to some influence emanating from the epithelial cells.

In the first place, one may assume that the chondrification is not an essential feature of the new growth from the beginning; in the case of the rectal growth there was no cartilage to be found in either the primary tumour or in the inguinal gland which was removed in a comparatively early stage of infection, whereas it was found in abundance in the recurrent growth when death occurred. So also with the chondrifying growth of the testicle, chondrification had apparently occurred in the centres of growth of oldest age; in those secondary formations which were apparently of most recent formation no suggestion of the presence of cartilage was to be found.

If, therefore, we attempt to trace the evolution of this variety of new growth, we have first the proliferation of the columnar epithelium, then the formation of the adventitious stroma in the neighbouring connective tissue, then, after a time, the appearance of myxomatous tissue in the stroma, and finally the development of cartilage.

And, whilst our information on the point is not complete, it appears highly probable that this chondrification of the stroma occurs almost exclusively in one variety of carcinoma, the columnar-celled.

Disregarding chondrifying new growths of the parotid gland, the exact nature of which is uncertain, and excluding the probably exceptional case of rectal carcinoma, it is rather remarkable that the remaining cases of chondrification which I have been able to cite have all occurred in malignant growth of epithelium developed from the cells

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of the Wolffian duct—that is to say, kidney epithelium, epithelium of the tubes of the rete testis, and the epithelium of somewhat ambiguous morphology which is believed to have belonged to the organ of Giraldés.

The occurrence of myxomatous tissue is more or less frequent in the stroma of columnar-celled carcinoma arising in other situations. This kind of tissue is frequently met with in, for example, carcinoma of the large intestine; and so far there is nothing peculiar in its association with columnar-celled carcinoma of the testicle, except, perhaps, that it is present more frequently, and is more conspicuous generally, than in the growths originating elsewhere. The peculiarity of the association of myxomatous tissue with malignant epithelial growths of the testicle and kidney lies in the fact that whereas in other tumours this kind of tissue generally undergoes merely a coarse mucoid change, which we may take to be of the nature of a degeneration, in these particular cases not only does the coarse mucoid degeneration occur, but in addition there may be in places a progressive development into a higher type of tissue.

Now, we have evidence that precisely the same appearance of myxomatous tissue in the stroma, with subsequent development to cartilage, occurs with probably equal frequency in the homologous innocent epithelial growth, the "cystic adenoma" which occurs in connection with the tubules of the rete testis. It is clear, therefore, that the development of cartilage in the stroma of the columnar-celled carcinoma has no essential connection with the malignant character of the growth; it depends rather upon some specific property of the constituent epithelial cells, some property of epithelium such as that of the tubules of the rete testis.

From the physiological point of view we may look upon a cystic adenoma of the testicle and a tumour or nodule of columnar-celled carcinoma as being to all intents and purposes ductless glands: in either case we have a closed system of tubules, lined by actively secreting epithelium, and supported by a connective tissue stroma.

Under these conditions it is easy to understand how retained secretion may escape from the epithelial alveoli and make its way into the interstitial spaces of the neighbouring

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stroma. And it is to the action of this escaping secretion on indifferent mesoblastic cells of the stroma that the development of myxomatous tissue in cases of columnar-celled carcinoma must be attributed.

Under various circumstances this myxomatous tissue has a certain tendency to develop into hyalin cartilage, as, for example, in the exceptional case of rectal carcinoma which I have described. Beadles (1) has recorded what is also apparently an instance of a similar change under other pathological conditions; in two cases of myxœdema minute masses of what was taken to be cartilage of a hyalin type were scattered through the lungs, and it appeared as if this cartilage had developed from small masses of mucoid tissue which were found in the lung.

But chondrification of this myxomatous tissue is of such frequent occurrence in both the simple and malignant epithelial growths which originate in the rete testis that we must suspect that the secretion of epithelial cells which are derived from the Wolffian duct has special properties which provoke this further stage of development in myxomatous tissue, the resemblance of which to developing embryonic tissue has already been commented on.

And it is not altogether surprising to find that the secretion of one cell may react with another cell in such fashion as to stimulate vital activity in the direction of development to a higher type of tissue. If we consider closely the development of the embryo it will appear probable, I think, that the earlier stages, at any rate, of cell differentiation and tissue development progress in response to stimuli of what we must somewhat vaguely term a bio-chemical nature.

The first definite stage towards development, the primary segmentation of the ovum and the histological differentiation of the elements of the inner and outer cell layers, can only be explained on the supposition that the entering portion of the spermatozoon, the male pro-nucleus, contains some substance, produced in the epithelial cells of the tubuli seminiferi, that has the property of stimulating the female cell to activity; and the further differentiation of a mesoblastic layer between epiblastic and hypoblastic cells may reasonably be believed to result from a stimulus conveyed by the products of the meta-

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bolic activity of the cells of one or other of the two primary layers.

And surely it is suggestive when we find that in after-life the products of the vital activity of cells descended from the cells of the Wolffian duct are capable of exercising such an influence upon myxomatous tissue of mesoblastic origin that the tissue undergoes development into hyalin cartilage, just as the embryonal myxomatous tissue changes to the hyalin cartilage which forms the basis of the developing bone.

I have elsewhere (7) insisted that the cause of occurrence and the nature of carcinoma is to be explained only by what we may term the "vital" theory, that the question is one which can be solved only by a study of the laws which govern, and the stimuli which excite, the growth of the body tissues generally. It has been pointed out how closely the malignant growth of epithelium follows the general histological characteristics of the normal cells from which it originates. And I may claim that a study of the process of chondrification in carcinoma suggests that not only do the specific cells of the carcinoma follow the histological characteristics of the normal epithelium from which they develop, but that in the manifestations of their biological activity also we may trace resemblance to the functional activity of their prototypes.

DESCRIPTION OF FIGURES.

PLATE VIII.

FIG. 1.—Section (× about 140) through a portion of the primary growth of columnar-celled carcinoma of rectum, showing epithelial tubules and closely-packed spindle-celled stroma.

FIG. 2.—Section (× about 140) through a portion of the infected left inguinal gland, removed by operation. The section shows epithelial tubules and a richly cellular stroma. The epithelial cells are undergoing a mucoid degeneration in places, the stroma also shows indications of myxomatous tissue. At the periphery of the drawing there is a mass of flattened and altered epithelial cells in a dilated tubular space.

PLATE IX.

FIG. 1.—Section (× about 52) through a portion of the recurrent growth as present at the time of death. There has been a development of typical hyalin cartilage in the stroma of the carcinomatous growth.

FIG. 2.—A portion of the same section (× about 140).

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A NOTE ON CANCER IN ICELAND.

By W. S. LAZARUS-BARLOW, M.D., F.R.C.P.

In the last report of the Cancer Research Laboratories a paper was contributed by Professor Sutherland on Cancer Statistics at the Mayo Hospital, Lahore. Owing to the great kindness of His Excellency the Danish Minister in London, of the officials of the Royal Board of Public Health in Copenhagen, and of Dr. Jonasson, the First Medical Officer in Reykiavik, I am enabled to place in contrast an account of the occurrence of cancer in Iceland.

In approaching the Danish Minister, the object was to obtain information concerning a region differing as much as possible from Lahore in point of race of inhabitants, climate, diet, general mode of life, etc. At the same time, it was desirable that the population should be relatively stable, and, as far as possible, uninfluenced by settlers from other lands. The insular character of Iceland and its distance from the common trade routes were in favour of a comparative absence of disturbing elements.

The information furnished to me is contained in two reports—(*a*) from the Royal Board of Health in Copenhagen and (*b*) from Dr. Jonasson. No doubt these two reports overlap one another to a certain extent since the Royal Board of Health probably derives its information through Dr. Jonasson. Nevertheless, supplementary series of questions addressed to Dr. Jonasson through the Danish Ministry have cleared up some obscure points. It does not, therefore, appear necessary to indicate the source of the information more in detail in the following paragraphs.

It appears that though cancer is still an uncommon disease in Iceland, it has been known at all times, and has been fairly equally distributed over the country. It has been

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associated with the same symptoms as elsewhere, and within a longer or shorter interval has ended in death after more or less severe suffering,

The Annual Reports furnished to the Royal Board of Public Health at Copenhagen from about the year 1866 onwards seem to indicate that before the year 1896 cancer was extremely rare; at any rate, its occurrence is not mentioned amongst the chronic diseases named in the reports. About the year 1896 several medical men reported the occurrence of "unusually many" cases. How far this is to be associated with the fact that in 1896 Dr. Jonasson requested the District Physicians "in future to furnish the Principal Medical Officer with quarterly lists of cases of disease" it is impossible to say. It must be added, however, in this connection, that no special reference to cases of cancer was made in this request, and therefore that no radical change was made in the method of recording them.

Below is given a table showing the numbers of cases of cancer recorded during the years 1890–1900, with the sites of the primary disease. In answer to inquiries, I learn that these cases are based on "clinical diagnosis," and that there is no means of determining how many were determined as the result of post-mortem or microscopic examination. From the regions that are noted as the seats of disease it is probable that carcinoma rather than sarcoma is the type of disease under consideration. With regard to the latter form of malignant disease, Dr. Jonasson says, "Sarcoma occurs occasionally in Iceland, but no more detailed information is available."

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TABLE I.

Table showing the total number of cases of Cancer reported in Iceland between 1890 and 1900 with the site of the primary disease.

YEAR.	Cases of Cancer.	Site of Disease.									
		Lip.	Tongue.	Face.	Œsophagus.	Stomach.	Liver and Stomach.	Intestine.	Rectum.	Uterus.	Breast.
1890	2	2	—	—	—	—	—	—	—	—	—
1891	2	—	—	—	—	1	—	—	—	—	1
1892	2	—	—	—	—	1	—	—	—	—	1
1893	1	—	—	—	—	1	—	—	—	—	—
1894	1	—	—	—	—	1	—	—	—	—	—
1895	4	—	—	1	—	2	—	—	—	—	1
1896	10	1	—	—	2	4	1	—	1	—	1
1897(α)	25	6	—	—	—	9	2	—	—	2	3
1898	19	—	2	—	—	12	—	1	—	2	2
1899	27	3	—	—	1	17	1	3	—	—	2
1900(β)	22	1	2	—	2	10	—	—	1	1	4
Totals	115	13	4	1	5	58	4	4	2	5	15

(α) The site was specified in 22 cases only.
(β) The site was specified in 21 cases only.

In connection with the above table it must be noted that since there are no medical men in "private" practice in Iceland the data are those for the entire population. Although from the evidence it is not clear whether the reported "cases of cancer" were *deaths* from cancer or *living* cases, or both, it will be convenient to give a table showing the annual mortality and the population of Iceland over the period of years 1890 to 1900.

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TABLE II.

Table showing the Yearly Population and Mortality above the age of 35 years in Iceland during the years 1890–1900.

YEAR.	Population.		Deaths above the Age of 35 Years.	
	Males.	Females.	Males.	Females.
1890	69,977		438	516
1891	33,301	37,193	407	282
1892	33,895	37,790	305	328
1893	33,351	37,870	318	334
1894	34,227	37,953	537	586
1895	34,819	38,630	268	281
1896	35,466	39,216	256	266
1897	36,044	39,619	328	322
1898	36,192	40,075	458	453
1899	36,303	40,080	417	392
1900	36,131	40,177	418	447

Although the comparison is not strict owing to the great differences in the characters of the figures included, it is interesting to note that in the year 1899, in which the largest number of cases of cancer is recorded, the ratio of recorded cancer cases at all ages to deaths above the age of 35 years is 27 : 809, *i.e.* 3·34 per cent. In London, according to the Registrar-General's returns for 1903, the ratio of carcinoma at all ages to deaths above the age of 40 years was 2,554 : 33,840, *i.e.* 7·55 per cent.

The most significant part of the reports on Iceland lies in the site of the primary disease. Even if we recognise to the full the difficulty of diagnosis of cancer of the stomach apart from actual inspection either at operation or at autopsy, it is remarkable that more than half the number of the cases recorded are said to affect the stomach, while only 20 out of

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the entire series of 115 cases affect parts other than the alimentary tract. So great a preponderance of alimentary cases, judging from the Records of The Middlesex Hospital, at least, only concerns the male sex, and although no details of sex or age are available in the Iceland cases, it is unlikely in view of the fairly even division of the population and of the mortality between the two sexes as shown in Table II. that the cancer cases themselves concern males exclusively or chiefly. Though one must speak with caution it seems very probable that Iceland shows an exceptionally large proportion of cancer of the alimentary tract as compared with the class of patients met with at The Middlesex Hospital.

In comparing the Iceland data with those from Lahore and from The Middlesex Hospital other points of interest are disclosed. The complete absence of recorded cancer of the penis in Iceland, with its frequency amongst Hindus, the infrequency of uterine and breast cancer (17·4 per cent. of all recorded cases for Iceland and 18·75 per cent. of all "carcinoma" at Lahore) compared with its frequency (50 per cent. of all carcinoma) at The Middlesex Hospital, the great relative frequency of cancer of the stomach and *upper* parts of the alimentary tract in Iceland, with its tendency to affect the *lower* parts of the alimentary tract in India, are points for consideration.

One is, however, unfortunately obliged to confess, in the case of both the Icelandic and the Lahore statistics, that the numbers of cases are very small, that information is wanting upon many important points, and that unaided by microscopic examination or autopsy, clinical diagnosis alone is still in many instances an unsafe guide. Nevertheless, though making all allowances for inaccuracy, it is important to recognise that three regions differing so widely as Iceland, Lahore, and The Middlesex Hospital, yield very different information concerning the site-incidence of cancer.

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Plate I.

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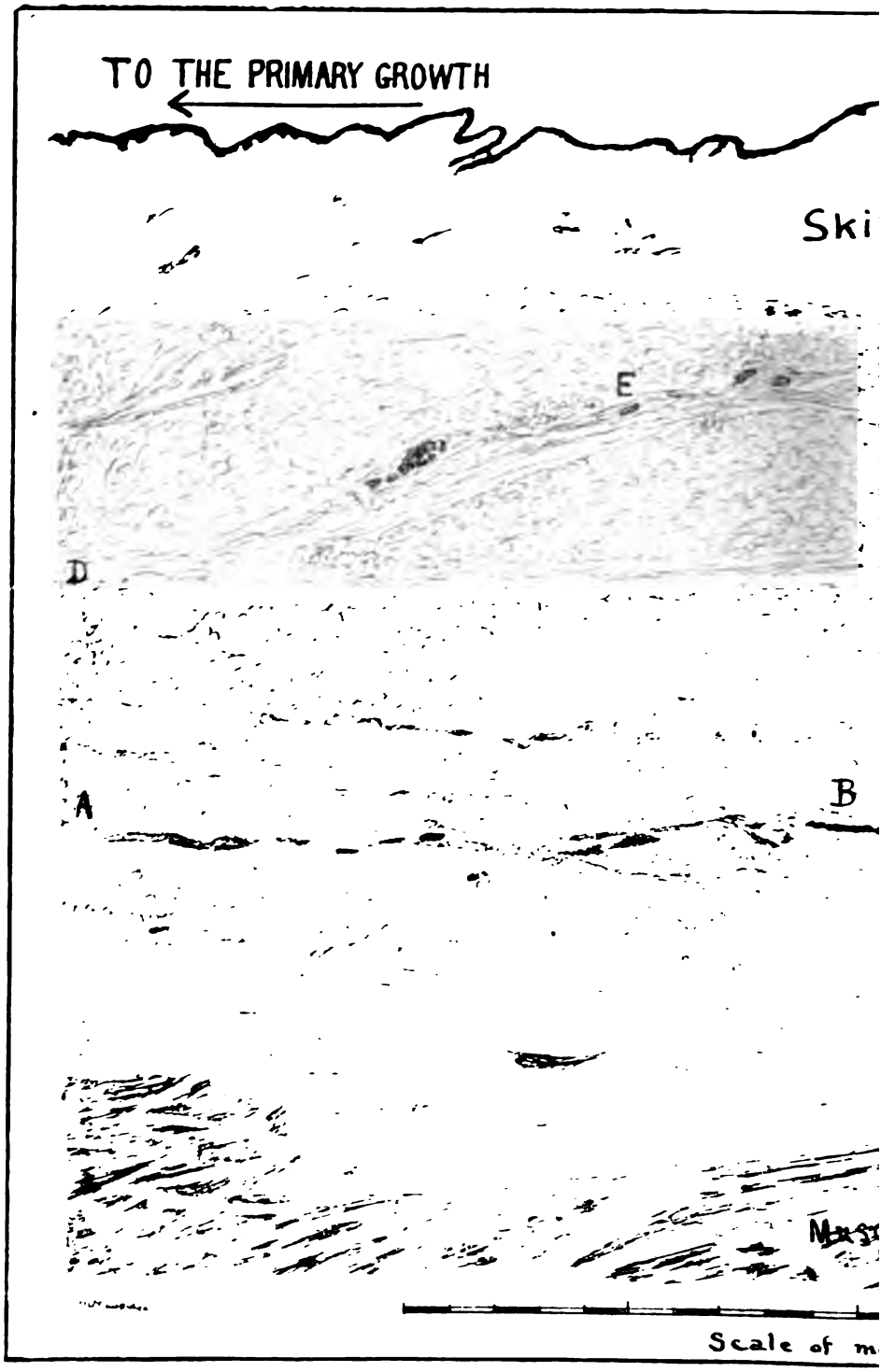

Fig. 2.—The microscopic growing e

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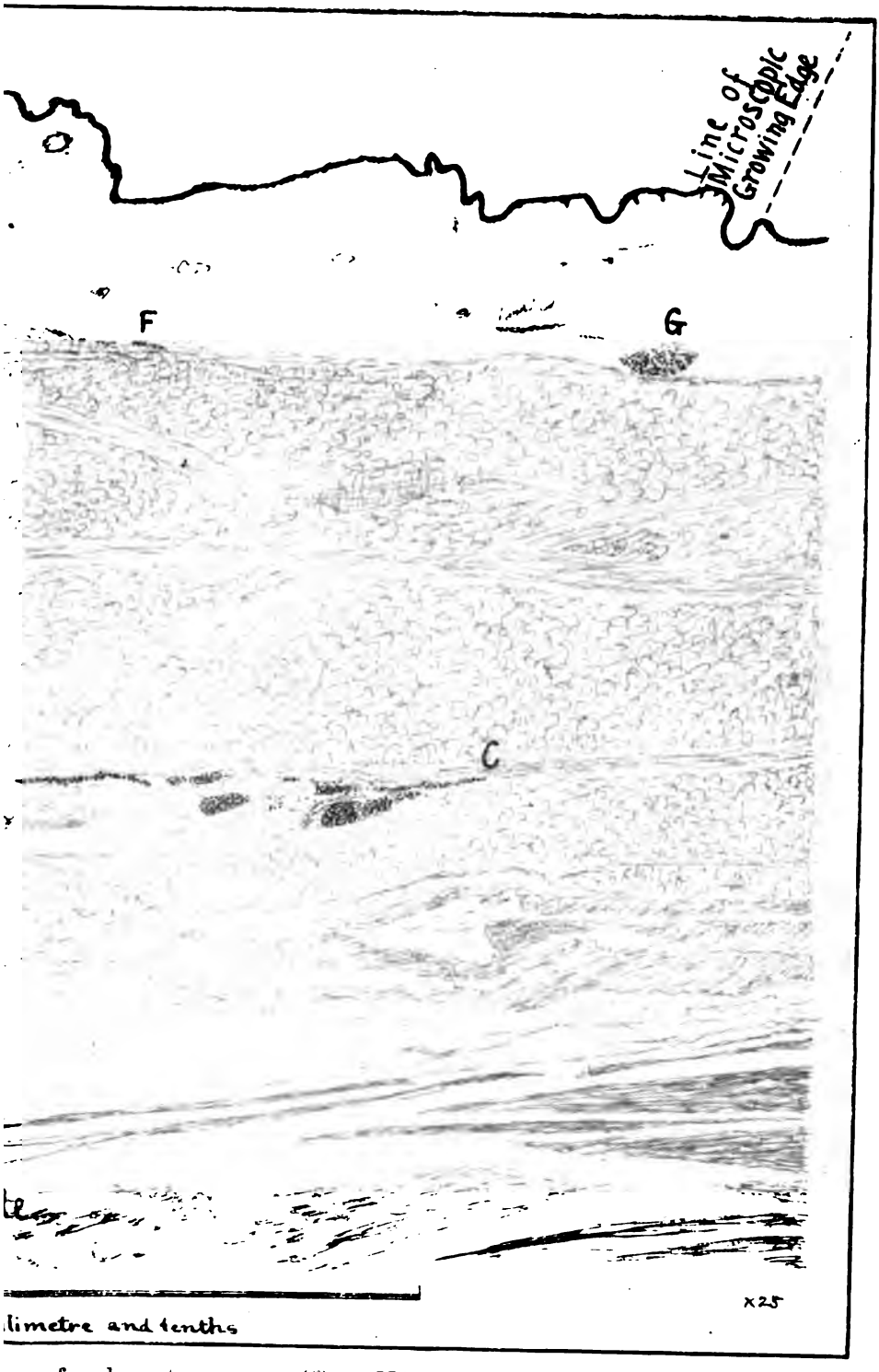

ge of a breast cancer. (Case II.).

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Plate III.

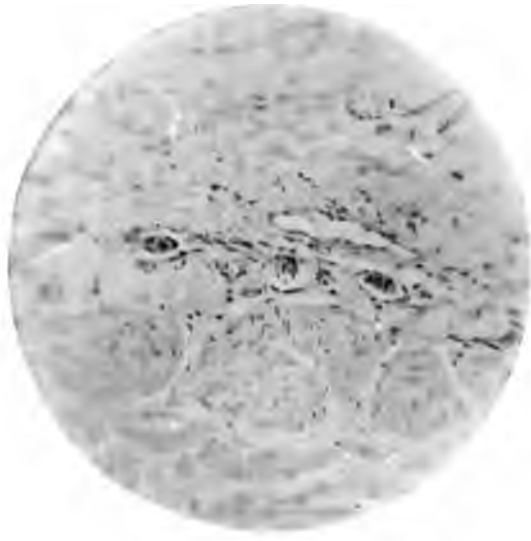

Fig. 3.

Fig. 4.

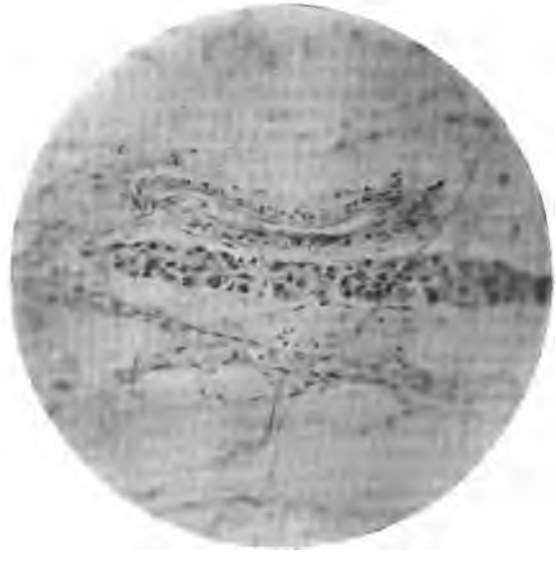

Fig. 5.

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Plate IV.

Fig. 6.

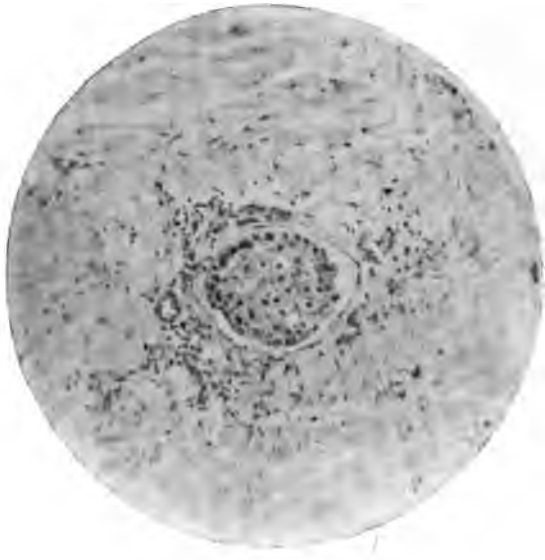

Fig. 7.

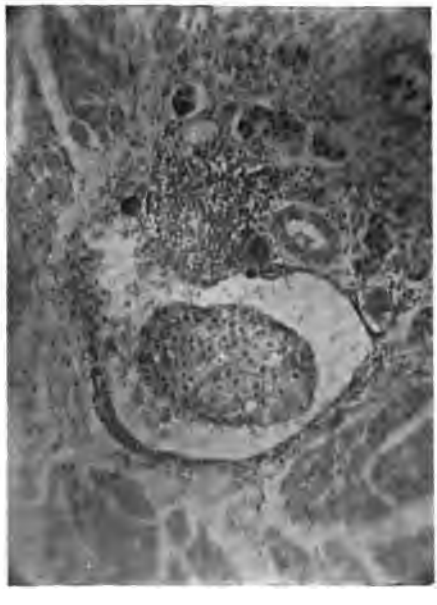

Fig. 8.

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Plate V

Fig. 9.

Fig. 10.

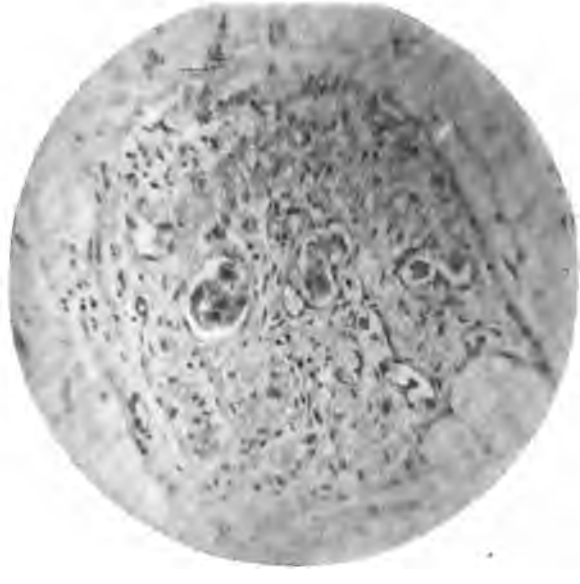

Fig. 11.

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Plate VI.

Fig. 12.

Fig. 14.

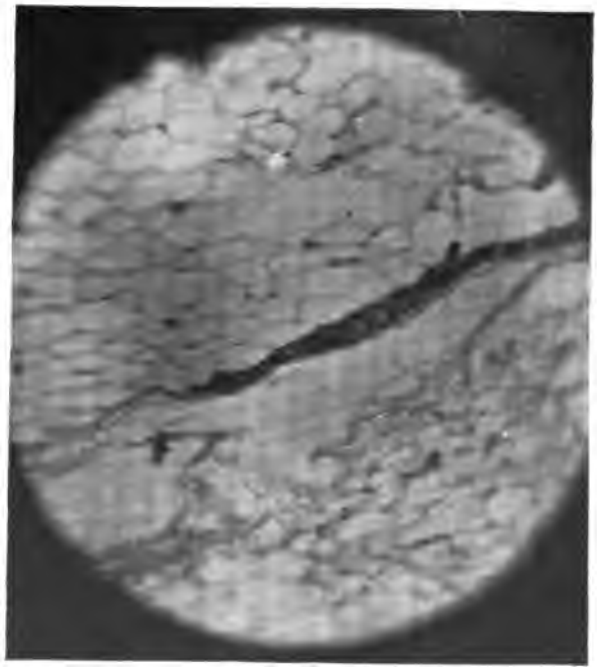

Fig. 13.

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Plate VII.

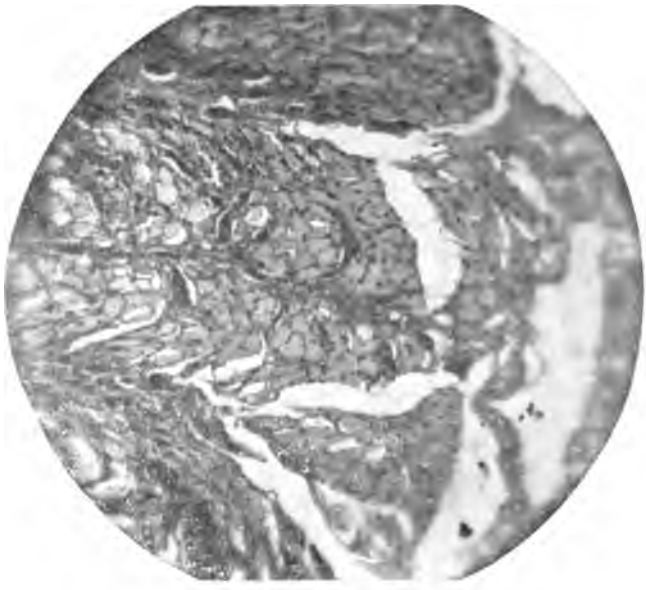

Fig. 15.

Fig. 17.

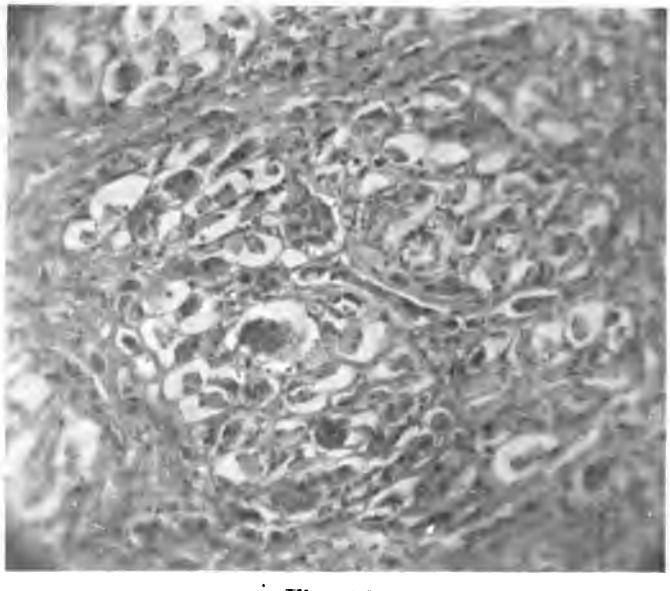

Fig. 16.

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Plate VIII.

Fig. 1.

Fig. 2.

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Plate IX.

Fig. 1.

Fig. 2.

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